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JANUARY 1943

VOL. VI ISSUED BI-MONTHLY NO. 1

PUBLISHED BY CHARLES C THOMAS

220 EAST MONROE STREET, SPRINGFIELD, ILLINOIS, U.S.A.

MAR 23 1943

JOURNAL OF NEUROPHYSIOLOGY

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Entered as second-class matter February 13, 1939 at the postoffice at Springfield, Illinois, and Menasha, Wisconsin under the Act of March 3, 1879

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CORTICAL RESPONSE OF THE ANESTHETIZED CAT TO GROSS PHOTIC AND ELECTRICAL AFFERENT STIMULATION*

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(Received for publication July 31, 1942)

INTRODUCTION

THESE EXPERIMENTS were undertaken to determine some of the general aspects of the cortical reactions to photic and electrical stimulation of the visual system in the cat. Bartley and Bishop (2) first observed that the response of the rabbit's cortex to electrical stimulation of the optic nerve consisted of a complex series of events. The cat's cortex, which is somewhat more interesting for purposes of analysis, has been explored in different ways by several experimenters. Kornmüller (12) observed that the spontaneous rhythms could be modified by photic stimulation, and that "on" and "off" responses could be superimposed on the rhythms. The extent of the cortical area which gave a more or less characteristic rhythm and definite responses was mapped. Gerard, Marshall and Saul (10, 11) made somewhat similar observations and explored the extent of the area giving visual response. They used concentric needle electrodes and a loud speaker as indicating device. They reported a larger area than that found by Kornmüller. Their area more nearly resembled that suggested by Poliak (20), including what he then labeled as striate and extra-striate visual cortex. Also in disagreement with Kornmüller's restriction of visual responses to area 17, Talbot (21, 23, 24) found "primary" visual responses in the cat to be evoked locally in both 17 and 18 by photic stimuli localized in the field. O'Leary and Bishop (18, 19) mapped the apparent visual projection area in the rabbit using electric shocks to stimulate the optic nerve. They found that both striate and an area usually considered to be parastriate were involved. Claes (7) reported observations on the visual system of the cat made on the isolated encephalon preparation.

The present experiments were essentially a continuation of the observations on the primary projection system of the somatic sensory system by Marshall, Woolsey, and Bard (13, 14, 26).

METHOD

Action potentials were led from the pial surface by cotton thread electrodes which were connected to a two channel cathode-ray recording system. The electrodes used were "monopolar," though many checks were done with "bipolar" leads subtending a short distance on the surface of the cortex, or vertically oriented on and within the cortex. The electrodes were held in a modified Horsley-Clarke stereotaxic instrument. Various kinds of photic stimulation were used. For many experiments a neon lamp driven by a pulse

* This work was supported in part by a grant-in-aid from the John and Mary R. Markle Foundation.

generator was employed. For others an incandescent lamp was focused on a translucent light scattering cover placed as a contact lens on the cornea, and the beam was interrupted by a rotating slit. The duration of flash was from 1 msec. upward. The inside of the cover had a brightness of 30 to 250 mL. and was equivalent to illuminating the entire visual field at these levels. Usually only monocular stimulation was used, but in some experiments both eyes were stimulated simultaneously with light of about the same intensity by splitting the beam from the incandescent lamp. Observations were also made on the cortical potentials evoked by stimulation of the optic nerve by single electrical shocks. Nembutal was usually employed as a general anesthesic, but in some experiments ether was used. Observations on the amplitude of the response, sensitivity, threshold, and latency were made at various depths of anesthesia. In the earlier experiments of this series the pupil was dilated by atropine: after it was observed that atropine had an exciting effect on the cortex (22) it was discontinued and hyoscine was used instead.

Intracortical and subcortical recording was accomplished by small steel suture needles insulated to the tip, or by electrodes consisting of No. 40 enameled stainless steel wire with an outside diameter of 75 micra. Since the Horsley-Clarke apparatus was constructed of stainless steel this electrode arrangement was relatively free from polarizing voltages. Points at which observations were taken were marked by a modification of the iron deposition method of Hess (15). For some of the observations the optic nerve was stimulated by single shocks. For this purpose the eye was resected, the retina cut off around the optic disc and the remnants of the retina were then tied to a silver wire. Another silver wire supported on a universal joint constituted the second stimulating electrode.

Results

The sign of the electrical response at the cat's cortex following photic stimulation is most typically, but not always, initially surface positive, and has a latency of 17 to 25 msec. Any stimulation of moderate to high intensity produced dorsally more than one surface positive wave, the interval between them being 40 to 80 msec. As many as 5 such responses often occurred, following a single brief photic stimulation. It is doubtful that a 2 msec. flash produces an "off" effect, but the multiple response occurs nevertheless (4, 22). Multiple responses are obtained even with long flashes 200 to 300 msec. in duration. While the analysis of the multiple response phenomenon is not the concern of this paper, it should be pointed out that it is readily elicited under anesthesia of such depth that spontaneous activity is negligible.

With nembutal anesthesia, there appear to be two general types of cat preparations based on characteristics of the cortical response. The first type is the most numerous and gives responses which are predominantly surface positive with a comparatively small negative component following each positive wave. The second type of preparation yields potentials in which the predominant phase is negative. Apparently either the negative wave may begin a few msec. after the initiation of the positive wave, and thus cancels a considerable part of the positive component of the response, or the positive wave may be intrinsically smaller. Occasionally the initial positive phase is insignificant. It occurred to us that this difference in characteristics might be correlated with the fact that some cats show an initial excitement stage while going into nembutal narcosis. In some of the animals this reaction is comparable to the reaction following morphine administration in the cat. We have, therefore, made it a point to compare the type of response to photic

stimulation in all cats which show this reaction, but there is no correlation. An example of the predominantly negative type of response is shown in Fig. 1-*2* and *8*, in which it is seen that the first response of the series is definitely diphasic with positive phase first. The second response is initially negative with an ensuing positive phase at certain points on the dorsal striate area. At other points it is negative with no appreciable positive phase. In some preparations all positive phases are small or negligible.

In general, however, in moderately or deeply nembutalized preparations the initial response is a definite positive wave. Under light nembutal anesthesia the succeeding negative wave is usually more prominent; if more anesthetic is administered (intraperitoneally or intravenously) the negative wave is usually reduced or obliterated, leaving the typical predominantly positive wave characteristic of most of the primary sensory reactions of the cortex in somatic, auditory or visual systems. Apparently, the negative wave of the response tends to be reduced by the barbiturates along with the spontaneous cortical potentials. The clearest demonstration of the difference between the positive and negative components in this sensory reaction is that shown by the picrotoxin-cocaine reaction of Curtis (8). The picrotoxin is applied to a spot on the striate cortex and after several minutes the initial positive wave is enhanced and a large negative wave develops. If a depressing agent such as nembutal is now applied on the same spot, the negative wave quickly disappears leaving the enhanced positive wave.

It is not certain that there is discharge over projections from the striate cortex to either the tectum or the suprasylvian gyrus in typical deeply anesthetized preparations in which the amplitude of the negative phase of the response is negligible. If picrotoxin is applied, however, the negative wave produced by the drug in the striate area is accompanied by obvious electrical responses or definite changes of activity in the tectal and pretectal region and on the suprasylvian gyrus. If nembutal is now applied to the same spot the negative wave disappears and the response observed in the tectum or the suprasylvian gyrus always becomes small and usually disappears. This relation is not always diagrammatically clear however, and some observations indicate that the negative wave apparently was eliminated in the striate area without completely eliminating the associated response which was initiated or facilitated by the picrotoxin. This may only mean that some negativity which still remains is cancelled out by the enhanced positive wave and so does not appear on the records. We have not thoroughly explored the thalamus and lateral geniculate for evidence that the cortical projection reaction initiated by picrotoxin is actually projected to those regions. Certainly, in the lateral geniculate it is not obvious, and this fact agrees with the lack of anatomical evidence that the striate projects to the geniculate of the cat.

The hypothesis that different mechanisms are responsible for the positive and negative waves is given support by observations on the interaction between two eyes. This has been done by electrically stimulating the

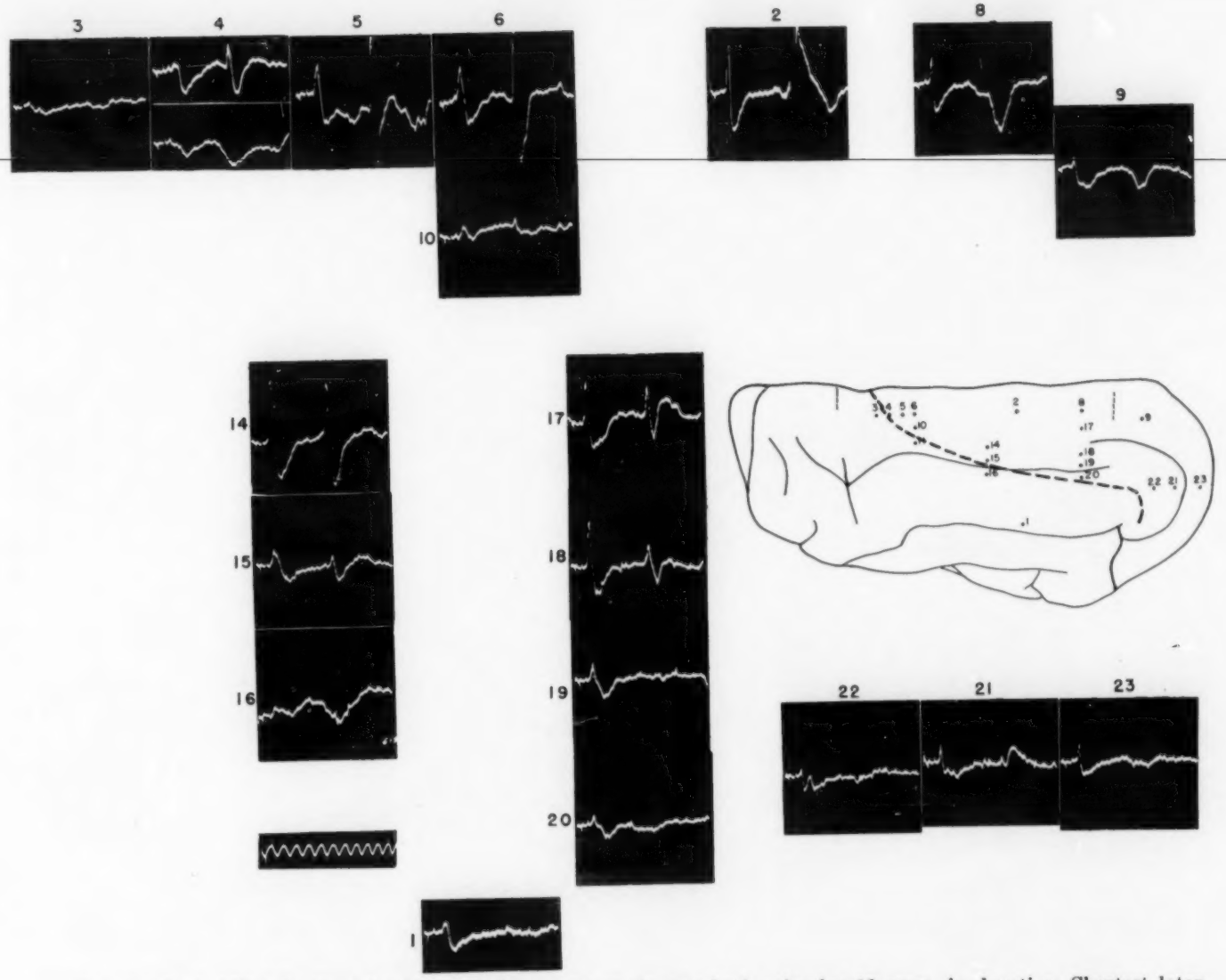
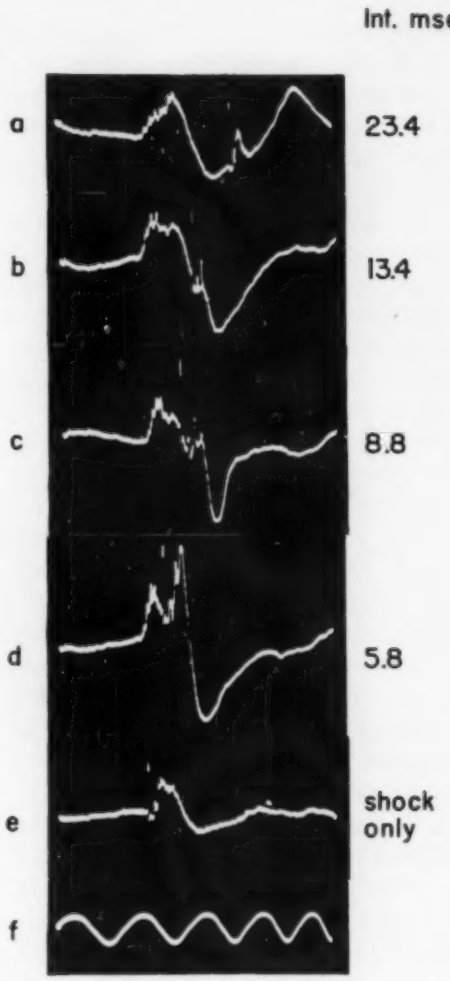


FIG. 1. Typical distribution of cat's cortical response to strong photic stimulus 10 msec. in duration. Shortest latency from start of stimulus to initiation of striate response about 17 msec. Note in record from point 2 that second response [illegible] negative. Record from points 8 and 9 entirely negative.

optic nerve on one side at various intervals before and after photic stimulation is applied to the other eye. If the photic response is approximately completed when the electrical shock is delivered at the opposite nerve, the surface positive cortical response to the latter is considerably subnormal, but



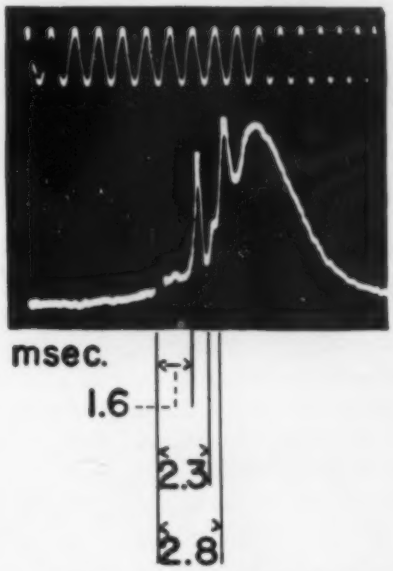


FIG. 3. Striate response to single shock applied to contralateral optic nerve. See text.

FIG. 2. Showing substantial degree of independence of the positive and negative response mechanisms. Photic response leading a response to single weak electric shock on the contralateral optic nerve. The intervals between the initiation of the photic response and the application of the shock are indicated at right of oscillogram. At *a* the positive phase of electric shock is subnormal and negative phase absent. *b* shows 4th component absent but negative phase enhanced. *c* more enhancement of negative wave with positive components about same as in *b*. *d* shows enhancement of last positive and negative phase. *e* is response to the electric shock only.

the negative wave following it may show significant enhancement both in amplitude and gradients of the waves. (Fig. 2).

The composition of the cortical wave obtained by photic stimulation is probably the result of algebraic addition and temporal dispersion of the spike wave series evoked by electrical stimulation of the optic nerve, Fig. 3.

The latter reaction consists of three spikes of axon time-dimensions, and a slower wave. The first spike starts with a latency of about 1.5 msec. The second is typically a smaller one occurring about 0.8 msec. after the initiation of the first spike, and on or near its peak the third spike begins. The third spike, perhaps also the second spike, is superimposed on the rising phase of the slow wave; and its peak occurs about 1.2 msec. after the beginning of the first spike. The slow surface-positive wave appears to start rising from the base line about the time at which the first spike process is concluded. It is usually followed by a more or less prominent negative wave, and, as in the case of the photic response, the negative wave is sometimes more prominent than the positive wave.

This spike wave is similar to that described by Bishop and O'Leary (5). There may, however, be a disagreement regarding what we designate as the second spike. In our records it almost always occurs as shown in Fig. 3. Occasionally on contralateral stimulation, but more often when the ipsilateral nerve is stimulated, and perhaps dependent on the position of the lead on the visual cortex, the second spike is temporally separated from the third spike so that it is clearly revealed as a distinct entity. The first and second spikes are both resistant to cortical depression produced by failure of circulation, application to the pia of hypertonic salt solutions, distilled water, or depressing drugs. Both exhibit short recovery times, and when the shock frequency is increased to 20 per sec. both of these spikes are attenuated much less than the succeeding cortical components. These characteristics suggest that each is a geniculate projection reaction. The first spike may represent the invasion of the cortex by the radiation reaction and the second may represent a similar process of a reaction which has been delayed in the lateral geniculate body by transference across interneuronal cells in that nucleus. However, electric shocks applied in the region of the optic radiations near the lateral geniculate produce the same spike pattern as is obtained by stimulation of the optic nerve. While this might result from antidromic effects, the probability is that the second spike is cortical in origin.

If a monopolar steel needle electrode insulated to the tip, or an enameled steel wire 75μ in diameter, is slowly pushed into the cortex, fairly definite discontinuities appear in the record at characteristic levels which can be identified by a suitable marking technic (15). On the surface of the pia the spike wave series is seen (Fig. 3). In the upper part of layer III or in layer II the slow surface positive wave is not recorded, in lower III or upper part of layer IV the surface positive wave is recorded as a smaller negative wave. The third spike is not recorded in lower III, and in the lower part of IV it is inverted. Within layer IV the second spike disappears and the first cortical spike shows reduced amplitude. Within the limitations of this evidence, these observations indicate that the fourth (slow) cortical component of the surface response is elaborated mainly in layers II and I, the third component in layers III and II, the second in layer IV and perhaps part of the first component also in layer IV.

The slow surface positive wave is composed of many smaller reactions algebraically added, each of which has a longer duration than the spikes which precede it. This can be seen when the frequency of the stimulus is increased to about 20 per sec., the first and second spike components undergo relatively little reduction, the third spike is seriously reduced, and the fourth component is very small and composed of fluctuating small waves. These wavelets sometimes fluctuate quite regularly, with a long period of about 7 sec., and may be correlated with similar fluctuations in components at the geniculate. When the stimulus is repeated at cycles of 1 per sec. or less, the fourth component often shows 2 or 3 definite inflections, suggesting that it is composed of reactions involving at least three systems of cortical neurons.

General distribution of responses

There is a striking difference between the amplitude of the response on the posterior half of the gyrus lateralis and the entire gyrus lateralis posterior. On the gyrus lateralis the positive wave is typically much larger than that on the gyrus lateralis posterior and the negative wave following the positive wave is relatively smaller. Observations on sections of brains of some of these cats indicate a significant correlation between the population density of larger cells in layers II and III and the amplitude of the surface positive wave.

The anterior boundary of the gyrus lateralis has been studied with some care and it has been found that electrical responses to photic stimulation occur within 2 or 3 mm. of the junctions of the ansate and marginal sulci, Fig. 1. The apparent visual projection area tends to follow the splenial sulcus as it curves upward at its anterior end. These observations have been checked with differential, or bipolar leads, one electrode being on the surface near the active area and the other just on the edge. The position of the anterior boundary is not a function of depth of anesthesia, whether nembutal or ether is employed. The identification of small responses is more difficult when spontaneous activity is intense, but average observations show that the fundamental reaction of the primary projection system is about the same, though negative components are larger and more definite in light anesthesia. The boundaries correspond closely. We have checked this cortical region anatomically by making small lesions in the ipsilateral cortex and observing retrograde degeneration in the geniculate 10 to 30 days later (Fig. 4). This evidence, while not invulnerable, agrees very well with the electrical evidence and indicates that the geniculate does project somewhat more anteriorly on the dorsal cortex than the maps of Campbell (6), Minkowski (17), and Kornmüller (12) indicate.

In nearly every experiment definite responses were found on the posterior half of the suprasylvian gyrus. Usually they are smaller in amplitude and often their latencies are the same as those of the striate area responses. These responses are seen not only when monopolar leads are used, as some experimenters have reported, but have been regularly observed with bipolar

electrodes oriented in several different ways. They are usually single in moderately deep nembutal anesthesia. The first type of response in the suprasylvian shows many of the characteristics of primary sensory reactions and agrees with the observations made with localized photic stimuli (24). Reactions of this type are particularly common over the entire posterior half of the suprasylvian gyrus. It has not yet proved possible to observe clear degeneration in the lateral geniculate following circumscribed lesions in the suprasylvian gyrus. If there is any such degeneration it is not obvious to us, and is certainly not comparable to the type seen following lesions in the striate area. This matter is still under investigation. However, when enough

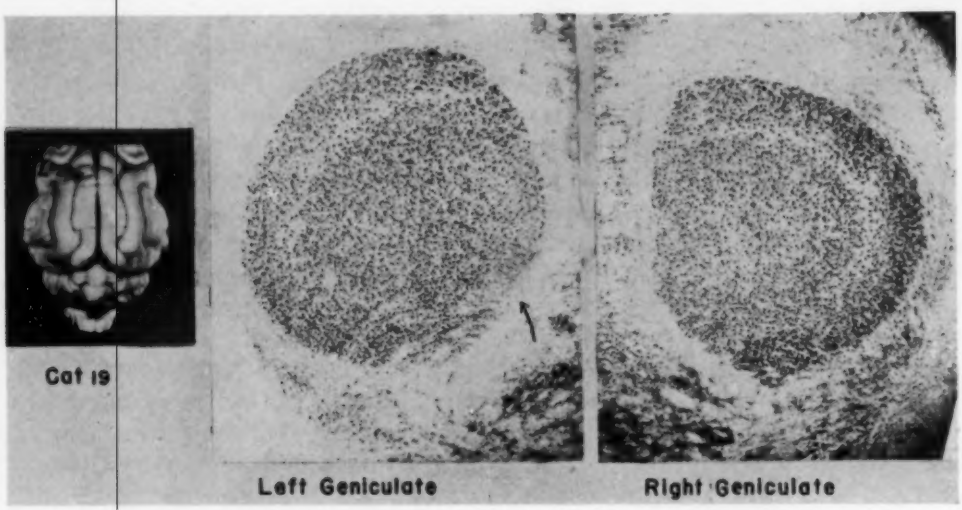


FIG. 4. Localized retrograde degeneration reaction in geniculate following lesion in anterior part of marginal gyrus as indicated in picture of brain in upper left. Arrow indicates degenerated region in left geniculate

time has elapsed following area striata removal for retrograde degeneration to be well developed in the lateral geniculate, responses to photic stimulation are no longer obtained from the suprasylvian.

At various regions of the suprasylvian gyrus, there is often present a second type of response which has considerable amplitude and a longer latency than the primary response. It typically disappears in deep anesthesia. This component is apparently due to activation of association fibers projected from the striate area to the suprasylvian cortex and can be clearly demonstrated by the picrotoxin-nembutal reaction as discussed above.

An area made up of the lateral middle part of the suprasylvian gyrus and often extending over onto the ectosylvian gyrus across the ectosylvian sulcus, shows a curious reaction. It is quite well localized in this region (region 1 on the chart, Fig. 1), whether electrical (Fig. 5), or photic stimulation is used (Fig. 1), and it is usually found ipsilaterally, as well as contralaterally to the

stimulated side. Its relation to the visual pattern has not been investigated. It persists after both striate cortices have been removed and the tectal region separated from the geniculo-thalamic region by a sagittal knife cut. The threshold to electrical stimulation is higher than that for the striate reaction, but is of the same order of magnitude. This reaction lacks the spike sequence of the striate reaction (Fig. 5).

Discussion

As many investigators have recognized, the phases of cerebral action potentials can be, at least, partly accounted for on the assumption that impulses approaching the electrode produce positive signs, those leaving the electrode produce negative signs, and that those approaching and passing the electrode show two prominent phases, plus another less prominent one, with positive phase usually first. These considerations become more complicated when the neurones (and hence the resulting dipoles) are short compared with the velocity and wavelength of the reaction, or in cases where strata of vertically oriented neurones may be involved as in the cortex. The proximity of a non-conducting boundary also enters into the situation. In all cases it is probable that the reactions sum to produce a higher potential when the electrode is just over the dipole stratum than when it is within it.

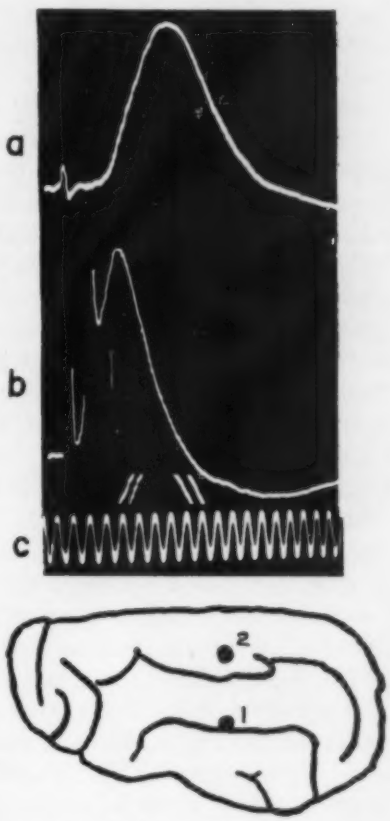


Fig. 5. Comparison of response from region 1 (a) and striate response (b) of the suprasylvian to electric shock to contralateral optic nerve. C is 1000 cycles.

It appears to us that these general considerations are just as applicable and, perhaps, more useful for certain problems than attempting to apply rigorously the theoretical treatment of Wilson, McLeod and Barker (25). The smallest electrode we used was 75μ which is sufficiently large to make killed-end effects significant, and these have the property of exaggerating the first positive phase of approaching reactions, relative to the negative phase of receding reactions. How significant this factor is we do not know, but we do not believe it is serious. It is worth pointing out that an electrode on the pial surface is virtually a dead end lead, and that one placed in a nucleus is somewhat similar in principle because of the synapse delay factor which temporarily separates the approaching and receding reactions.

If the dipoles produced by these respective reactions are of a sufficient magnitude, as is the case when recording from the lateral geniculate, the optic tract reaction there and the succeeding radiation reaction may each be the theoretical triphasic spike series with the one major phase of each reaction reversed (see also 16).

Pending further information we suggest that the records indicate that the fourth component can be attributed to activity in the plexiform layer I, the third component to layers II and III and the second component to layer IV. The first component may be considered to be elaborated by radiation endings. The probability is that the second component is the result of synaptic activation of a short dipole confined to layer IV. Negative waves, recorded on the pia, are recorded in reverse phase in the lower layers of the cortex. This agrees with the idea that the ascending electrical processes are surface positive and the descending processes are surface negative.

Exactly what enters into the synthesis of the fourth or wave-like component we cannot say. It is composed of at least three components, and perhaps one of these may arise from the long cell processes which enter the plexiform layer. The tangential component of the reaction in the plexiform layer should be significant for reactions involving this layer. This wave is summed of activities of neurones having longer time parameters than those of the spike-producing neurones. It should be also recognized that, perhaps, in these systems the factor of synapse-time may be radically different than that concerned in the spike reactions. The latter may all have a finite synapse-time similar to that of the geniculate, or the IIId nerve nucleus. Synapses of the free axon ending types, on the other hand, may have a variable transmission time which under certain conditions of excitation may be zero. This variability would permit temporal dispersion to play a greater role in the elaboration of wave-like responses and hence collaborate in the summation of reactions of small potential into smooth wave shapes.

The fact that photic stimulation sometimes evokes responses which are entirely or predominantly surface negative indicates that under certain conditions, which have not yet been defined, the negative or corticofugal reaction overshadows the positive component, or that the positive components are lacking. Electrical shock stimulus applied to the optic nerve, however, shows that the first three (spike) components are always present and positive. This is probably true also for photic stimulation, but the temporal dispersion, in this case, conceals the detail. The fourth or wave-like component, however, sometimes exhibits only a small positive component which may be followed by a large negative wave, or the negative wave may obviously begin during the rising phase of the positive component and thus partially cancel it. The negative wave, when at its maximum, has a much higher electrical amplitude as indicated by the strychnine and picrotoxin reactions. Hence, it is clear that under favorable conditions for excitation of the corticofugal neurones or descending intra-cortical pathways, and with the temporal dispersion associated with photic responses, that the negative

component of the reaction may completely mask the positive components. While in general, we believe it is correct to speak of the negative reactions as indicating corticofugal activity, it is obvious that descending intracortical reactions would be accompanied by surface negative signs whether the projection neurones are activated or not. There is also the possibility, mentioned by Adrian, that activity propagated tangentially in the cortex may exhibit negative waves. The promptness with which nembutal abolishes the negative picrotoxin reaction suggests, in this case, that the reaction is coupled through the plexiform layer. It is possible, however, that other negative reactions are initiated without the participation of the plexiform layer. This would help to explain why the positive phase is sometimes missing.

Another factor of equal importance in the relative size of the negative phase, is the summation interval of the neurones participating in the negative reactions. The interaction illustrated in Fig. 2 shows this over a fairly short interval. Much longer intervals can regularly be demonstrated by the picrotoxin reaction, if a multiple response to photic stimulation is occurring. When three or more successive surface positive responses are following each flash of light, and when picrotoxin has been applied to the surface of the cortex, the characteristic picrotoxin (or strychnine) effect is seen first on the last response. A few seconds later it moves to the next response, and so by steps, it advances to the first response. This indicates that the positive reactions exert a cumulative effect on the excitability of the neurones involved in the negative response, and that such summation may extend for at least 300 msec. It follows that after several conditioning volleys of thalamic or other origin, that the corticofugal mechanisms may be activated by a comparatively small stimulus. Hence, the positive component may be so small that it is not seen. This may be significant in instances in which "spontaneous" waves of the cortex are, apparently, entirely negative. It also explains why a more prominent negative phase is often seen in the second or third response when the responses are multiple and, also, why the "off" response is often predominantly negative as in Fig. 1, *2* and *8*.

Our employment of picrotoxin to produce corticofugal discharges is, in principle, merely a modification of the technic so brilliantly employed by J. G. Dusser de Barenne and his collaborators. Our method of using these drugs is more similar to that of Bartley, O'Leary and Bishop (3); and our application of the method originated with Curtis (9) who found that application of strychnine to the surface of the pia usually enhances any reaction already present and often produces large negative components where none existed previous to the application. The important fact was that under conditions of repetitive stimulus at, say, 1 per sec., the strychnine response tied in with the response to a peripheral tactile stimulus. An area of the somatic sensory cortex, for instance, which was the locus of a surface positive response following a peripheral tactile stimulus, will, after application of the strychnine, yield an enhanced surface positive wave immediately followed by a large negative wave which is in turn accompanied by responses in other

loci of the cerebrum to which association fibers are projected from the strychninized area. This phenomenon differs from that of the Dusser de Barenne school in that, if the stimulus is repeated at a set frequency (often as low as one in 10 sec.) few or no uncontrollable spontaneous strychnine discharges occur in preparations anesthetized with usual dosages of nembutal or dial. That is, the system is now equilibrated and operating in a quasi-stationary state. Each stimulus cycle causes the entire response cycle to repeat the pattern recurring with nearly or quite the same characteristics on the successive cathode ray traces. Curtis (8) also applied cocaine to the same spot and thereby temporarily abolished the negative phase of the convulsant drug reaction. This makes it possible conveniently to turn the corticofugal mechanisms on and off. The advantages of this technic for certain types of experiment are obvious.

Curtis tested several excitants (9) and found that picrotoxin is slow to act, but is the most potent, and that its effect persists for several hours; metrazol acts rapidly, but the effect persists for only a few minutes; and strychnine acts in 5–15 min. and persists for 30–40 min. Picrotoxin in conjunction with nembutal has been regularly used for these experiments. It is worth pointing out that this technic reduces the necessity of using several parallel recorders with continuous film and triangulation to locate the areas or regions actually reacting. This follows because the reaction is recurring on the oscillograph tubes in approximately the same pattern for each successive stimulus and the "spontaneous strays" which sometimes occur can be immediately identified. In the meantime, electrodes can be moved about usually with assurance that the actual pattern of activity is neither moving to other loci or significantly changing in any other characteristic.

Regional responses

In the case of both photic and electrical stimuli the cortical responses of greatest amplitude are found in the mid-dorsal region of the lateral gyrus. This includes a region where the characteristic striate architecture is well developed and a region where cell stains show a high population density of the large cells of layers II and III. The gyrus compositus or post-lateral gyrus rarely produces surface positive waves of an amplitude comparable with those recorded from the mid-dorsal region of the lateral gyrus. This gyrus appears to have fewer large cells in layers II and III and the strata appear to be thicker. Further, factors bearing on this peculiarity of the difference in response amplitudes will be discussed by one of the authors in a paper dealing with the problem of localization (see also 22, 23).

On the lateral gyrus the anterior limits of the electrical response, and also of the geniculate projection as indicated by retrograde degeneration, suggest that geniculate projection extends over a greater area than indicated by the classical structural definition of the area striata. Admittedly the electrical reactions near the margin may represent intra-cortical transmission, but we do not believe they are physical artifacts. Retrograde cell de-

generation is subject to error when applied to this sort of problem because of the possibility of incidental injury or thrombus posterior to the region excised. The sections show no evidence of this, however, and the degenerated region in the lateral geniculate occurs where it should, according to the plan suggested by Minkowski (17), on the rostral and ventro-medially directed tip of the lateral geniculate. It cannot be stated that the definitely extrastriate response of the cat is not relayed through the geniculate. The accurate geniculo-striate relation must be examined more carefully. O'Leary and Bishop also found a somewhat similar situation in the rabbit (19) but concluded that the "parastriate" area there was really striate. Our area of potentials resembling primary projection reactions is somewhat larger than that reported by Gerard, Marshall, and Saul (19) but it agrees rather well with their data. Our area also more closely resembles the area defined by Poliak (20) than it does the area defined as striate by classical anatomical definition. More data on this will be presented in a forthcoming paper (24).

Part of the reactions on the suprasylvian gyrus have many characteristics of primary projection reactions, and part of them are obviously due to projection from the striate area. The fact that part of the suprasylvian reactions persist immediately after removal of both striate cortices and section of collicular bound pathways, indicates some projection either from the lateral geniculate or from possible nuclei near the geniculate. The failure of the suprasylvian reaction after retrograde degeneration of the geniculate, suggests that the geniculate is involved in some way which is not yet clear, possibly bifurcation of path, or that some other retrograde degeneration process has directly affected the suprasylvian or some relay nuclei involved.

This reaction is similar to the response produced in the medial ectosylvian surface by an auditory click stimulus. The areas in which the visual and auditory responses are obtained do, in fact, overlap in the medial and dorsal part of the ectosylvian gyrus, an area considered to be in the primary projection area of the auditory systems (1), but we have never observed maximum potentials from each at the same point in the ectosylvian, nor auditory responses of this type in the suprasylvian. Interaction between the auditory and visual responses has been tested in cases in which they clearly overlapped and, also, in separate loci on the ectosylvian, and none have been found. Neither stimulus conditions the response to the other in these preparations. Apparently the neurones are separate even in areas in which both responses are recorded from the same electrode. This means that the overlap is only apparent and not physiologically real, for, at least, the positive responses. This conclusion is suspicious and demands further inquiry.

Summary

1. A brief photic stimulus evokes, under several types and stages of anesthesia, one or more (multiple) cortical responses. A single electrical stimulus applied to the optic nerve does not evoke a multiple response of the type which follows photic stimulus.

2. The responses are usually predominantly surface positive, positive phase first. In light anesthesia negative components are prominent.

3. Application of 0.1 per cent picrotoxin to the pia enhances the positive component about 25 per cent and either initiates a large negative component or greatly enhances one already present. The positive and negative components are obviously due to separate neural processes. The positive component is associated with ascending cortical processes. The negative component is associated with descending neural processes. With picrotoxin it can be demonstrated that the negative wave is associated with activation of association areas and tectal regions. Application of nembutal to the same pial surfaces abolishes the negative wave and the projected reaction.

4. The separateness of the positive and negative processes can also be shown by cross conditioning of the cortical mechanisms, wherein a photic stimulus applied to one eye is succeeded by an electric shock applied to the opposite optic nerve. The positive components evoked by the latter reaction are subnormal, but the negative component may be greatly facilitated.

5. Facilitation of the negative-wave-producing mechanisms may build up over a period of several hundred msec. This is strikingly shown by the multiple response, with or without picrotoxin. The third or fourth component of a positive multiple response may be followed by a definite negative wave. If the excitability of the negative wave mechanisms is raised by picrotoxin, or by decreasing anesthesia, the negative wave moves by steps to the first primary response.

6. Electrical shocks applied to the optic nerve evoke in the cortex three positive spikes of axon dimensions. These are followed by a slow positive wave, which in turn is typically followed by a negative wave. The amplitude of the negative wave is subject to the factors discussed above.

7. The first two spikes in the cortical record are very resistant to depression by chemicals or subnormality due to repeated activation at frequencies above 10 per sec.

8. Both photic excitation of the retina and electrical excitation of the optic nerve evoke primary responses over both striate and extra-striate (or peristriate) regions.

9. The extra-striate reactions in the suprasylvian are of two types. One type is obviously due to activation of association pathways from the striate. The other exhibits characteristics of the primary projection reactions and appears to be relayed from the lateral geniculate or nuclei close to the latter.

10. It is possible to assign to particular cortical layers the components of the response to electrical stimulation of the optic nerve.

11. The predominant negativity of the photic cortical response in some cats cannot yet be adequately explained.

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THE EFFECT OF SKELETAL FIXATION ON SKELETAL MUSCLE*

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(Received for publication September 24, 1942)

MUSCULAR inactivity resulting from destruction of the motor nerve is accompanied by a number of well known but little understood phenomena. Of these atrophy, fibrillation and hypersensitivity to acetylcholine and potassium are the most outstanding. Cutting the spinal cord also results in cessation of voluntary muscular contraction. Muscles thus affected show no fibrillation but do exhibit an atrophy which is, in the initial stages, as marked as that due to section of the motor nerve (16). Hypersensitivity to acetylcholine is also present but is less pronounced than in the case of the fibrillating "denervated" muscles.

Both upper and lower motor neurone lesions result in a marked decrease in the activities of the muscles involved. A precise evaluation of the effect of immobilization alone on muscles with completely intact motor and sensory nerve pathways is attempted in the present experiments.

The disuse atrophy of skeletal muscle has long been recognized clinically. In 1776 John Hunter (6) mentioned and in 1854 James Paget (11) described such atrophy associated with pathological conditions of the joints.

Experimental disuse atrophy has been brought about by tenotomy (13, 9, 8, 2, 18) and by cast fixation (5, 7, 8, 17, 1). The former method is accompanied by a bizarre contracture (2, 18) and the latter may be complicated by the pressure of the cast on the muscles and blood vessels and the "weight-bearing" which is possible, to some degree, in most casts (17). The so-called disuse atrophy produced by isolation of the section of the spinal cord supplying nerve fibres to a muscle (18, 4, 12) may be complicated by other factors as a result of severance of nerve pathways to the muscle.

The object of the present experiments was to test the effect of a method of immobilization which would not be open to these criticisms and to follow the course of any resulting disuse atrophy in an experimental animal in which the time-course of atrophy due to other causes had been investigated.

METHOD

Rats weighing from 175–250 g. were used. Light ether anesthesia was employed during all operative and experimental procedures. The knee and ankle joints of the limb on one side (different sides in alternate animals) were fixed with steel pins. The object of the fixation was to prevent skeletal movement due to contraction of the gastrocnemius-soleus group of muscles and to maintain the bones in such a position that these muscles would not be stretched. In fixing the ankle joint the foot was placed at right angles to the lower leg and a pin was forced up through the bones of the foot into the tibia or the periosteum and connective tissue on the anterior aspect of this bone. The knee was fixed with the tibia at right angles to the femur by a pin forced through the knee joint into the tibia. The

* Aided by a grant from the National Foundation for Infantile Paralysis, Inc.

pins were cut off below the skin and, if necessary, a single suture was used to close each wound. Figure 1 shows a roentgenogram of a limb with the pins in place. The early operations were performed with the aid of x-rays and a fluoroscopic screen but this was later deemed unnecessary. The limbs were examined frequently and if fixation was incomplete this was remedied at once by inserting a new pin. Operating instruments and the pins were kept in alcohol prior to use and although no other antiseptic precautions were taken very few infections were encountered.

Pinning of the joints involved by the muscle being investigated was found to be a most satisfactory method of immobilization and was employed in most of our experiments. Clin-

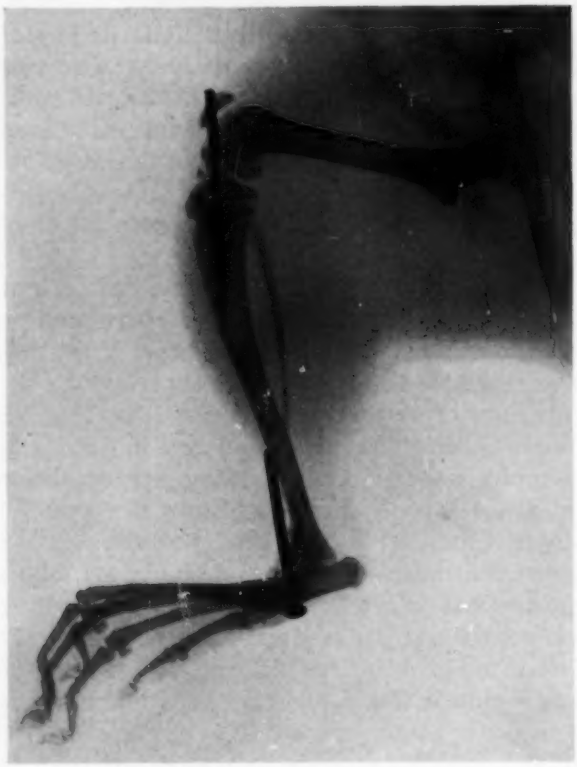

FIG. 1. Roentgenogram of fixed limb with pins in place.

ical literature contains many suggestions that joint damage produces trophic effects on muscle not attributable to simple disuse. Contrary to this belief, however, a small series of animals with cast immobilization showed atrophy which was quantitatively similar to that produced by pinning.

In every experiment a large group of animals was employed and representatives taken at random for testing as required. As a rule the muscles were tested for fibrillation by the electrical method (14) and their acetylcholine sensitivity evaluated subsequently (10). This latter was accomplished by injecting 0.5 cc. of aqueous acetylcholine bromide solution into the exposed abdominal aorta or into each iliac artery, using a No. 32 needle and a tuberculin syringe. The concentration of the solution was increased with each injection until the sensitivity of both normal and fixed muscles was determined. The dilutions used are indicated on Fig. 3. The so-called full-strength solution contained 10.0 mg. of acetylcholine bromide per cc. The volume of each injection and the rate of injection were kept constant. Reaction of the muscles was recorded simultaneously on a smoked drum by means of isometric levers connected to the Achilles tendons which had been cut free from the foot.

In most experiments the motor nerves to the muscles were cut just before the test for acetylcholine sensitivity was made. Control experiments indicated that this procedure produced no immediate change in sensitivity. The elimination of reflex activity permitted a cleaner record being made. Before cutting the nerve neuromuscular continuity was tested by pinching the nerve or by electrical excitation of the nerve.

At autopsy the site of the pin at the knee was examined. Injury to large nerves or blood-vessels was never found. Finally, the gastrocnemius-soleus muscle groups from each side were carefully dissected out, blotted to remove any superficial moisture, and weighed immediately.

Results

Figure 2 indicates the degree of weight loss in the muscles affected by skeletal fixation. The weight of the "fixed" muscle (F) was divided by the weight

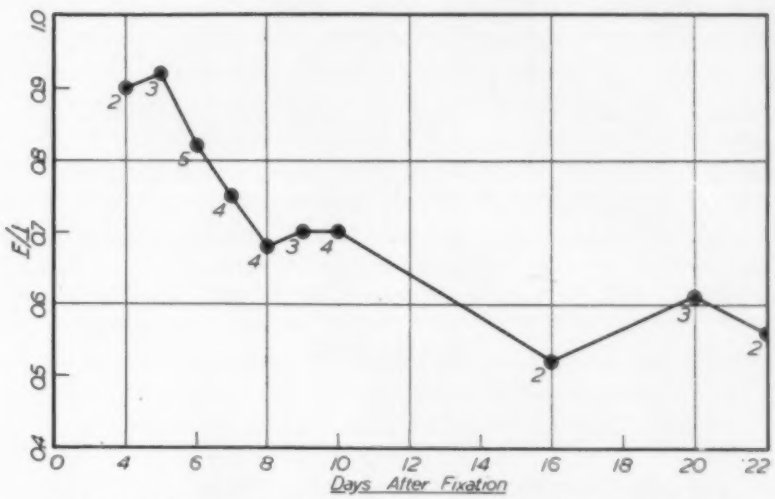

FIG. 2. Change in weight of gastrocnemius-soleus muscle group following limb fixation. Atrophy is represented by the decimal fraction of the ratio F/I where F is the fresh wet weight of the muscles on the fixed side and I that of the corresponding muscles on the normal side. The figure adjacent to each point indicates the number of animals contributing to the average represented by the point.

of the muscle on the normal side (I) and this quantity was plotted against the time in days after the operation.

The atrophy was very marked during the first 10 days and was about as great as that seen at the same time in muscles with the motor nerves cut (15) or in those deprived of upper motor neurone control (16). After the 10th to 14th day the atrophy no longer progressed but no significant reduction in atrophy was regularly observed. Whenever an animal was autopsied and showed a muscle weight indicating that regression of atrophy had occurred the joint-fixing pins were found to have become loose thus permitting some movement. The gastrocnemius muscles atrophied to from 50 to 60 per cent of the weight of the muscles on the control side in from 10 to 14 days. They then remained at or near this reduced weight for the duration of the experi-

ment (a few animals, not shown in Fig. 1, were carried on up to 41 days) in every case in which the fixation remained adequate.

No fibrillation was observed at any time in the muscles involved by the skeletal fixation. These muscles, as shown in Fig. 3, demonstrated a marked increase in sensitivity to intra-arterially injected acetylcholine as compared with either the muscle on the normal side or with muscles in completely

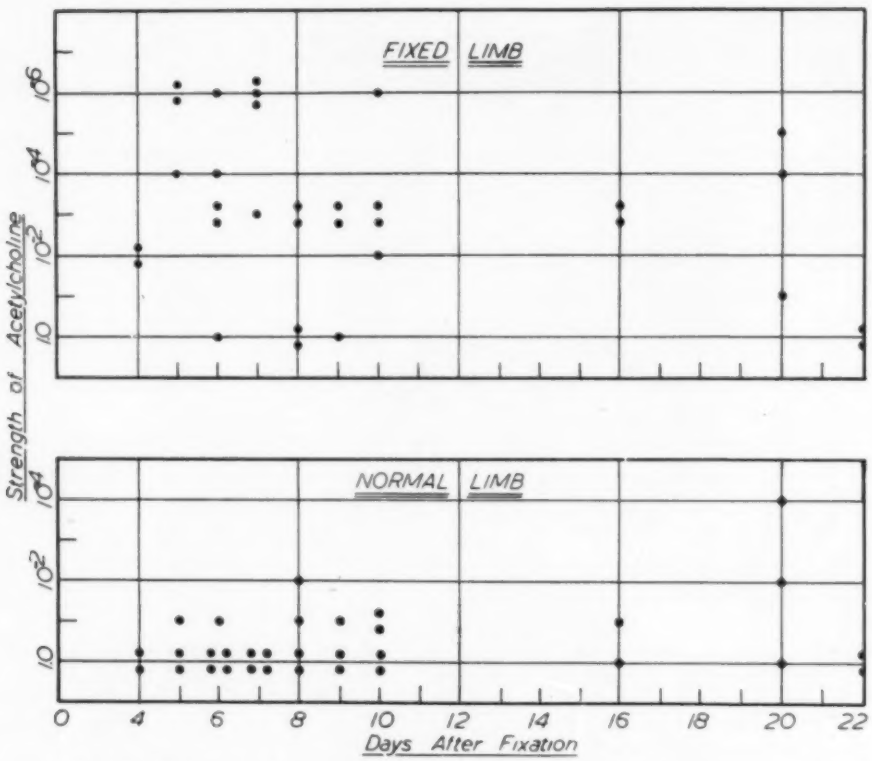

FIG. 3. Strength of acetylcholine required to elicit a response from the gastrocnemius-soleus group of muscles in fixed (upper diagram) and normal (lower diagram) limbs. The "full-strength" solution, indicated as 1.0, is such that 5.0 mg. of acetylcholine bromide are injected in the 0.5 cc. dose given. The other strengths contain proportional amounts as indicated and are administered in the same volume. Each animal sacrificed contributes one point to each diagram.

normal animals. The muscles involved by skeletal fixation did not show as marked an increase in acetylcholine sensitivity as do muscles deprived of their lower motor neurone (16). The increase in sensitivity reached a maximum about 10 days after the operation and thereafter the sensitivity tended to return towards normal although the atrophy was maintained.

DISCUSSION AND CONCLUSIONS

The outstanding features associated with denervated muscle are the fibrillary activity, the atrophy, and the hypersensitivity to intra-arterially

injected acetylcholine and potassium. Fibrillation has never been observed by us in any immobilized muscle with an intact motor nerve. On the other hand, both atrophy and increased sensitivity to acetylcholine are seen in muscles with normal activity prevented by skeletal fixation or by section of the spinal cord (15, 16). It has been suggested by Denny-Brown and Pennybacker (3) that fibrillation is due to the hypersensitivity to acetylcholine and other experiments (10) have indicated that potassium may have a causative role. The fact that fibrillation is not seen in animals with the spinal cord cut or with the limb bones fixed may be due to the fact that the acetylcholine hypersensitivity induced by these procedures is never as great as that seen in denervated muscles.

Cutting the motor nerve to a muscle prevents all activity of the muscle except fibrillation. Fixing the parts of the skeleton which are normally moved by the muscle merely makes muscular contraction futile. Observations on the series of animals thus treated leads us to believe that the animal quickly adapts to the altered skeletal mechanics and ceases to employ the muscles rendered useless. These muscles may be contracted occasionally but, after the 2nd postoperative day, they are usually flaccid and apparently toneless. Cordotomy (16) prevented voluntary contraction of the muscles of the hind limbs. These muscles appeared to be relaxed and showed little tone most of the time. They were, however, capable of violent reflex contraction when properly stimulated.

All three types of experiment yield muscles which atrophy and show hypersensitivity to acetylcholine. Both these features are most marked and most permanent when the motor nerve is cut. Functionally one feature common to the three types of atrophic muscles is that they are not subjected to a normal amount of tension-producing activity. Fibrillation involves little increase in muscle tension. Lack of tension-producing activity may produce or contribute to the atrophy. Thompson (17) has shown that the marked atrophy obtained by splinting a rabbit's limb in a cast may be very largely prevented if the cast is so applied as to permit "weight-bearing." This observation may account for failure by others (8) to produce marked atrophy by simple immobilization. Fixation by pinning permits weight-bearing through the bones alone and prevents the muscles under consideration playing any part in such activity.

It is not clear what the connection is between the lack of tension-producing activity, the atrophy and the acetylcholine sensitivity. It is, however, an interesting and possibly an important observation that immobilizing a limb produces the same kind of changes in the muscles involved as does denervation of these muscles. This finding suggests that the methods of treating paralyzed muscles which involve immobilization should be re-examined and possibly modified.

Summary

Skeletal fixation in rats was found to produce atrophy and hypersensitivity to intra-arterially injected acetylcholine in the involved gastrocnem-

ius-soleus group of muscles. The atrophy was initially as marked, but did not progress as far, as that seen in muscles paralyzed by the loss of their motor nerve supply. The atrophy produced was sustained for the duration of the experiment in all animals in which the fixation was maintained.

We should like to thank Professor C. H. Best for the kindly and helpful interest which he has shown in this work.

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INTRAVENOUS POTASSIUM, CALCIUM AND MAGNESIUM AND THE CORTICAL ELECTROGRAM OF THE CAT*†

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(Received for publication October 6, 1942)

ALTERATIONS in concentration of potassium and calcium in the blood stream may on occasion influence brain potentials (3). Since these ions affect both cardiac activity and blood pressure (7, 8, 13, 16), it is possible that some of the effects on the brain potentials which have been previously described are secondary to cardiovascular changes. In the present study an attempt is made to distinguish between those effects of potassium, calcium and magnesium ions on the cortical electrogram which are independent of cardiovascular disturbances and those which are regularly associated with them.

MATERIAL AND METHODS

Sixteen cats under light nembutal anesthesia (35 mg. per kg. body weight, intraperitoneally) were used in these experiments. The left hemisphere was exposed and brain potentials recorded simultaneously from two or three areas, using lead solder electrodes 3 mm. in diameter. A reference electrode was attached to the left ear. The areas of the brain on which the electrodes were placed in the various experiments are indicated by the heavy dots of Fig. 1. Although the simultaneous patterns from different areas of the brain were quite independent of one another, effects were not restricted to any one area of the brain. Simultaneous electrocardiograms were recorded from lead II. Grass amplifiers and ink writing undulators were employed to record the cortical electrograms and the electrocardiogram.

An isotonic solution of calcium chloride, potassium chloride, or magnesium sulfate was injected continuously into the right femoral vein. Five cats received injections of potassium chloride, five received calcium chloride and six were given magnesium sulfate. In two instances a control injection of isotonic saline was given prior to the main infusion. The rates of injection of each salt, usually about 15 cc. per minute, was sufficiently rapid to induce the characteristic sequence of electrocardiographic changes known to be associated with a progressive increase in concentration of the ions in serum (7, 13, 16). Injections were continued until death from cardiac arrest. Artificial respiration was carried on throughout the experiments in which magnesium was injected. In previous experiments it has been found that, when potassium is given, the mean arterial blood pressure does not change significantly until the onset of marked intraventricular block or cardiac arrest (8). Blood pressure is unaffected by calcium injection until the moment of arrest or of ventricular fibrillation. Magnesium, on the other hand, produces a progressive decline in blood pressure beginning soon after the injection is begun, before any electrocardiographic

* A preliminary report was presented before the American Physiological Society, at the Boston meeting, March 31–April 4, 1942. *Fed. Proc. Amer. Soc. exp. Biol.*, 1942, *1*: 76.

† Aided by grants from the Fluid Research Fund, Yale University School of Medicine, the Ella Sachs Plotz Fund and the Committee on Therapeutic Research of the American Medical Association.

‡ Honorary Fellow in Physiology, Yale University School of Medicine, May-September, 1939.

changes are manifest. It has, however, been shown that, despite this decline of pressure, there is no general cardiovascular collapse until intraventricular block or cardiac arrest appear in the electrocardiogram. It has therefore been assumed that cerebral anoxemia due to circulatory failure did not occur with calcium and potassium injections until signs of serious derangement appeared in the electrocardiogram. It is quite possible that, with magnesium, some failure of cerebral circulation due to declining blood pressure may have preceded important electrocardiographic changes.

Results

(i) *Potassium chloride.* No changes in the cortical electrogram could be demonstrated until intraventricular block or cardiac arrest had appeared.

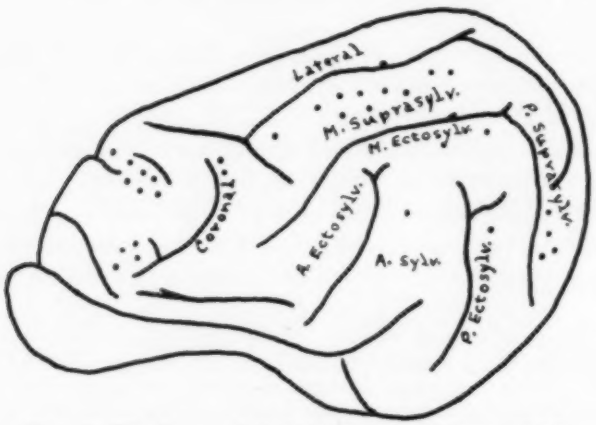

FIG. 1. The heavy dots indicate points from which records were obtained in various experiments.

After these cardiac changes were manifest, certain changes in the cortical electrogram did appear. These consisted of the development of large slow waves, sometimes preceded by temporary increase in the number of fast waves. The fast waves eventually disappeared, leaving only random slow waves, which persisted for some minutes after complete cardiac arrest.

(ii) *Calcium chloride.* Usually little or no change could be detected as long as cardiac action remained fairly normal, although in one experiment there was a little slowing. After disruption or cessation of cardiac action the higher frequencies disappeared from the cortical electrogram, and the amplitude and frequency decreased progressively until only slow random baseline swings were demonstrable.

(iii) *Magnesium sulfate.* Anoxemia due to respiratory failure was prevented by artificial respiration. In spite of this, the cortical electrogram was modified before any considerable change in the electrocardiogram was demonstrable (Fig. 2). There was a marked initial slowing (Fig. 2, 20 sec.), followed by restoration of the initial frequency (Fig. 2, 60 sec.). Later, with the development of auriculo-ventricular and of intraventricular heart block (Fig. 2, 120 sec.), slowing of the cortical electrogram reappeared together with a disappearance of the rapid waves.

Synchrony between electrocardiogram and cortical electrogram appeared in the experiment illustrated in Fig. 2. It developed first at 90 sec. in one brain area and at 110 in the other. By 150 seconds it had disappeared from the first region. This phenomenon has been described previously by Gerard, Marshall and Saul, who suggest that it may be due to local pulsations in the cerebral vessels (5).

(iv) *Sodium chloride.* In two experiments 30 cc. of isotonic saline were

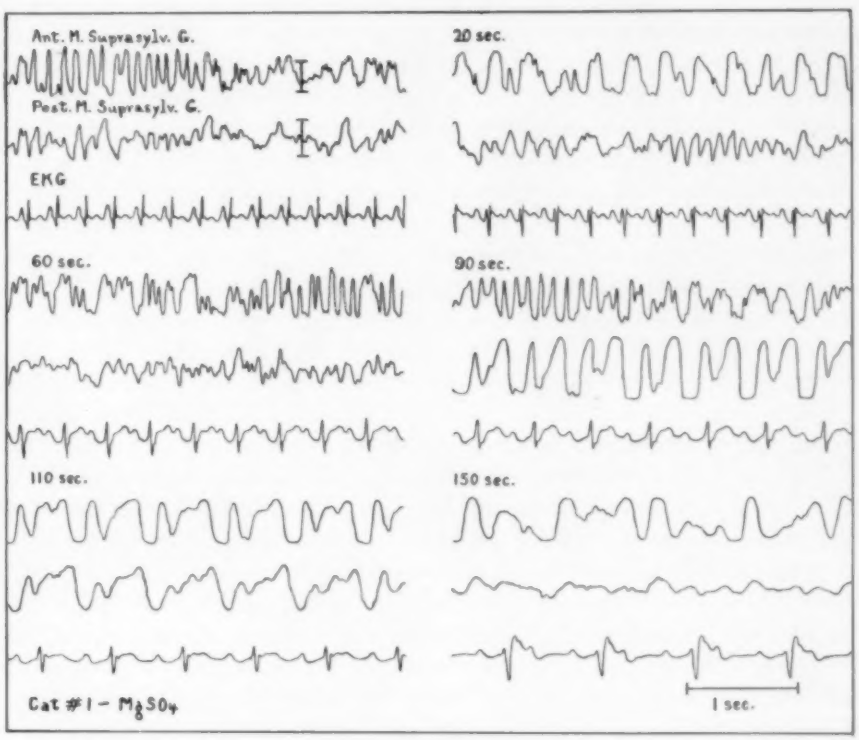

FIG. 2. Cortical electrograms and electrocardiogram at various times during the continuous intravenous injection of magnesium sulfate in the cat. The height of I corresponds to 50μV.

injected prior to infusion with magnesium sulfate. The rate of injection was the same as that in the other experiments. Neither the cortical electrogram nor the electrocardiogram was influenced by this procedure.

(v) *Post-mortem potential changes.* In these experiments potential changes in the brain continued for at least 15 minutes after complete respiratory and cardiac arrest, irrespective of the particular ion responsible. This persistence of electrical activity is shown in Fig. 3. In this experiment potassium had been injected until cardiac arrest had occurred. It can be seen that the random, slow potential changes 6 minutes after cardiac arrest are indistinguishable from those being recorded at the time of cardiac arrest. The electrical

activities of the two brain regions represented by the two records are quite dissimilar. Both destruction of the brain tissue directly beneath the electrodes and application of water to the surface of the brain altered the pattern of the cortical electrogram indicating that the potential changes are not artifacts. Other control experiments demonstrated that they did not depend on the character of the electrodes or of the amplifiers themselves. During

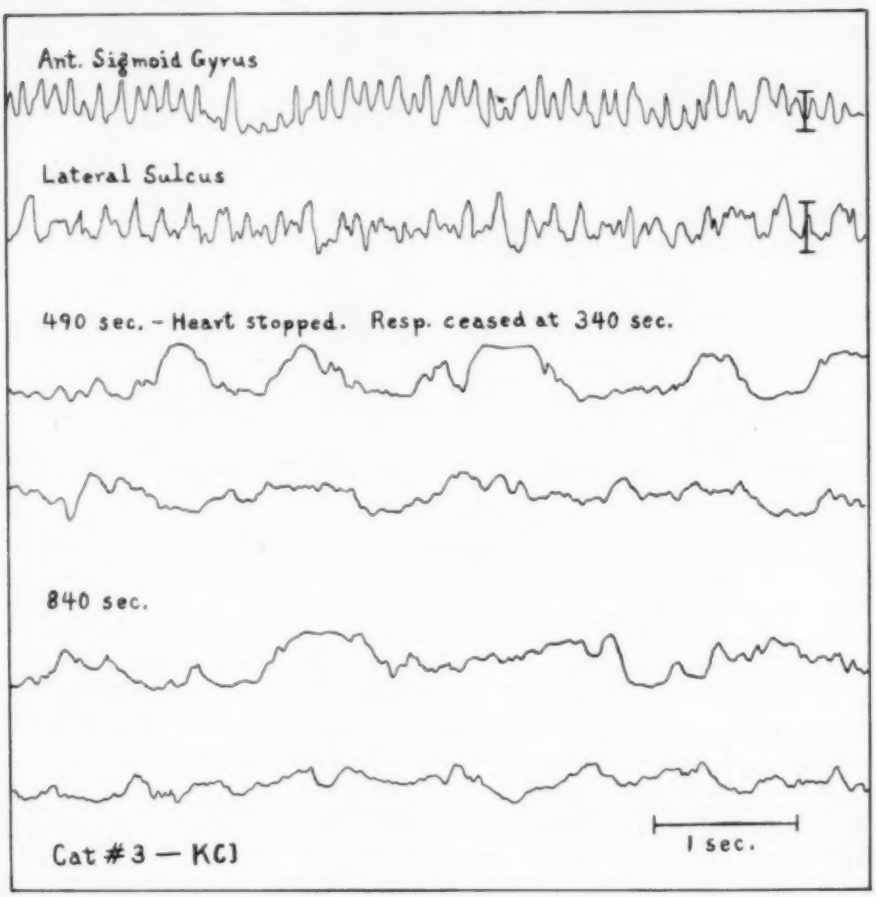

FIG. 3. Cortical electrograms prior to infusion of potassium chloride solution (top records) and at intervals after cardiac arrest and respiratory arrest. The height of I corresponds to 50μV.

this period of post-mortem electrical activity, pinching the foot, moving the paw, or pricking the footpad of the cat failed to evoke any response in the cortical electrogram.

DISCUSSION

Potassium and calcium, under the conditions of these experiments, exerted no distinct effect on the cortical electrogram until development of

terminal cardiac failure. The anoxemia resulting from the failing circulation may well account in a large measure for the cortical electrographic changes observed during the injection of these ions. The effects of magnesium are more difficult to interpret. The early, transient changes in the cortical electrogram appear with amounts of magnesium well within the limits of cardiac tolerance, but nevertheless sufficient to depress the blood pressure. These early effects might therefore be due either to a direct effect of magnesium on the brain potentials, or they might be secondary to the fall in blood pressure. The fact that magnesium, in concentrations within physiological limits, may directly affect the central nervous system sufficiently to produce surgical anesthesia, is consistent with a direct effect upon brain potentials, but from our experiments there is no way of deciding which explanation is the correct one. The secondary slowing of the cortical electrogram associated with electrocardiographic changes is comparable to the terminal effects observed with potassium and with calcium.

During the course of this study the coronal, the anterior and posterior sigmoid, the middle suprasylvian and the middle and posterior ectosylvian gyri were explored. The electrical activity from these different regions exhibited a high degree of independence. (see Fig. 2). Relative independence of various brain areas under different experimental conditions has previously been described (11, 14).

Anoxia alone, produced in a variety of ways, causes complete disappearance of brain potentials in the cat within one minute (1, 2, 5, 9, 12, 14, 15). The persistence of electrical activity in the central nervous system for some minutes after cardiac arrest was therefore rather unexpected. The reasons for this unusual persistence of brain potentials are still obscure.

Our observation that potassium has little demonstrable effect on brain potentials before its cardiac effects are manifest seems inconsistent with a statement by Emmens and Marks that potassium chloride, injected intravenously or intraperitoneally in mice, kills by an action on the central nervous system (4). They base this conclusion on the statement that death in their experiments occurs with convulsions and evident respiratory distress while the heart continues to beat. We have repeated their experiments, in addition obtaining continuous electrocardiographic records until death. In our experiments a period of cardiac arrest or of marked intraventricular block regularly preceded the convulsions and respiratory distress. Electrocardiographic complexes, presumably corresponding to mechanical ventricular beats, were occasionally observed after respiratory failure. These should not, however, be considered evidence of an adequate circulation. Since the cardiac changes were sufficiently severe of themselves to be responsible for death, it seems unnecessary to postulate an additional effect upon the central nervous system. We are thus unable to confirm their conclusion that the heart is not the primary cause of death.

Summary and Conclusions

1. The cortical electrogram and the simultaneous electrocardiogram of

the cat were followed continuously during the intravenous injection of salts of potassium, calcium and magnesium.

2. Potassium and calcium produced no changes in the cortical electrogram until the development of intraventricular block or of cardiac arrest. Subsequently slowing of the cortical electrogram developed.

3. Magnesium produced transient periods of slowing before pathological changes appeared in the electrocardiogram. A secondary slowing of frequency, much like that following cardiac arrest due to potassium or calcium, appeared after the development of intraventricular block.

4. Brain potentials persisted for at least fifteen minutes after complete respiratory and cardiac failure.

5. In concentrations tolerated by the intact cat, potassium and calcium are without demonstrable effect on the cortical electrogram while magnesium does have some effects.

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THERMOREGULATORY PATHWAYS IN THE CAT BRAIN STEM*

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(Received for publication October 20, 1942)

THE HYPOTHALAMIC regulation of body temperature (4) is effected by little known pathways which descend through the brain stem and spinal cord to innervate the somatic and autonomic effectors concerned in this activity. Some information on the brain stem distribution of these pathways has been provided by Keller (2) and Blair and Keller (1), who have studied the temperature regulation of cats and dogs with chronic section of parts of the midbrain and pons. They have found that heat maintenance activity can be entirely eliminated by transverse section of the medial quarter segments of the cephalic midbrain, while at the pontile level heat-loss activity is eliminated by sections involving only the lateral portions of the brain stem.

The present report is concerned with a further study of thermoregulatory pathways in the brain stem of the cat after more restricted lesions made with the Horsley-Clarke technique.

METHOD

Using the Horsley-Clarke technique (3) electrolytic lesions were produced in a series of cats, and 2 to 5 weeks after operation, the animal's temperature regulation was examined during a 3-hour period in an icebox at 34°, and in a hotbox at 120°, and compared with the results of preoperative tests. All temperatures are in degrees Fahrenheit, and all animal temperatures were taken rectally. At autopsy the position and extent of the lesion were verified microscopically.

LESIONS OF THE ANTERIOR MIDBRAIN

At the level of the anterior part of the midbrain, lesions in different animals destroyed the tectum and parts of the central and tegmental regions.

Tectal region. Aspiration of the tectum of the superior colliculus, except for its most lateral portions, produced no impairment in temperature regulation. A tectumectomized cat, tested 2 weeks after operation, elevated its body temperature slightly during a 3 hour period in an icebox, and showed typical piloerection and shivering. When its body temperature was raised in a hotbox to 103.9° (preoperative threshold, 104.1°), it panted with a respiratory rate of 250 per min., showed good sweating on all footpads, and exhibited evident dilatation of the ear vessels.

Central region. In cat 1, the lesion shown in Fig. 1A interrupted the central grey matter and the periventricular paths contained within it, yet the animal preserved perfectly normal regulation against heat and cold. Four weeks after operation it kept its temperature at a normal level during 3

* The authors wish to express their appreciation to H. W. Magoun for aid in preparing the manuscript and to Mary Ranson for preparing the figures for publication.

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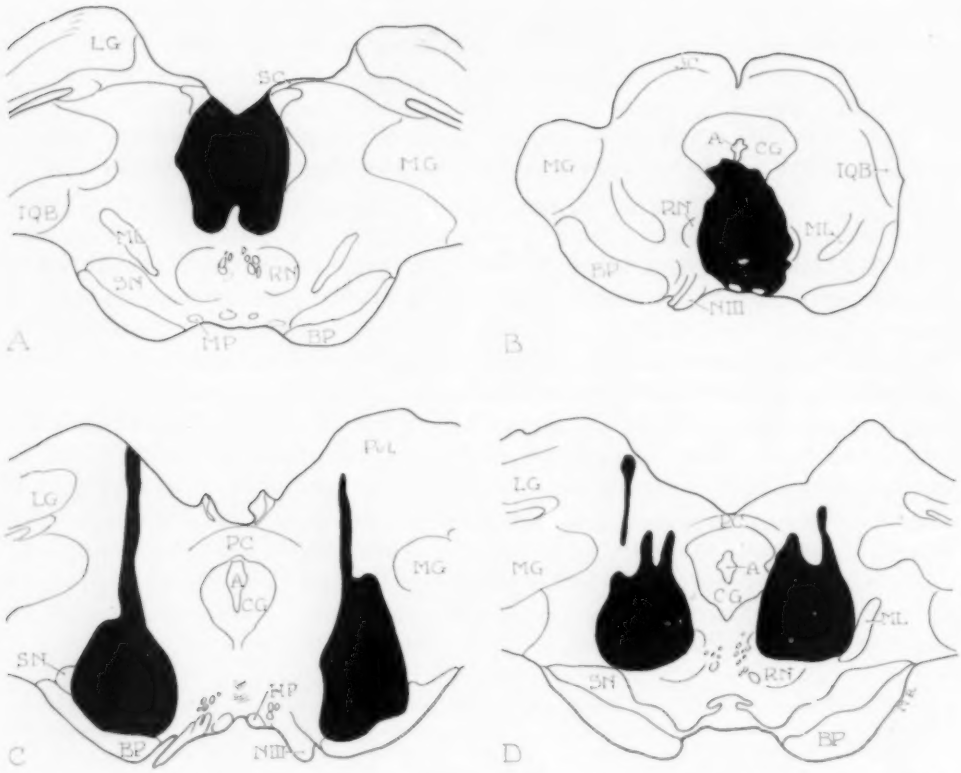

FIG. 1. A–D. Levels through the anterior portion of the midbrain showing the widest extent of the lesions in Cats 1–4, respectively. Abbreviations for all figures are as follows:

A	aqueduct	NIII	third nerve
BP	basis pedunculi	NVI	sixth nerve
BrP	brachium pontis	NVIII	eighth nerve
CG	central grey	P	pyramid
HP	habenulopeduncular tract	PC	posterior commissure
IC	inferior colliculus	PO	pons
IQB	inferior quadrigeminal brachium	Pul	pulvinar
LF	medial longitudinal fasciculus	RN	red nucleus
LG	lateral geniculate body	SC	superior colliculus
MG	medial geniculate body	SO	superior olive
ML	medial lemniscus	SN	substantia nigra
MP	mammillary peduncle	Trap	trapezoid body
NMV	fifth motor nucleus		

hours in an icebox and exhibited good piloerection and shivering. When its body temperature was raised in a hotbox to 102.5°, the animal panted at a respiratory rate of 240 per min. and showed pronounced sweating on all footpads.

In cat 2, a lesion destroyed the ventral part of the central grey and the medial region between it and the base of the brain (Fig. 1B). During a 3 hour period in an icebox, 3 weeks postoperatively, this animal defended itself normally against cold, exhibiting marked piloerection and some shiver-

ing. In the hot box it sweated a little and panted between rectal temperatures of 104° and 106° (preoperative threshold, 104.4°). Panting was irregular and spasmodic, however, and the respiratory rate did not increase above 180, whereas the animal's preoperative panting rate was 240 per min.

Tegmental region. Cat 3 with the bilateral lesions of the ventral tegmentum, substantia nigra and basis pedunculi shown in Fig. 1C, when tested 3 weeks postoperatively, maintained its body temperature during a 3 hour period in an icebox and exhibited good piloerection and slight shivering. In a hotbox it showed pronounced sweating on the footpads and panted, but at a higher threshold and with a slower respiratory rate than in the preoperative test.

Cat 4 with bilateral destruction of more dorsal parts of the tegmentum (Fig. 1D) raised its body temperature a little during a 3 hour period in an icebox and showed definite piloerection and slight shivering. When the animal's temperature was elevated to 106° in a hotbox, its respiratory rate increased to 100 per min. but no panting occurred. There was no sweat on any pad, and the animal felt cool as though no vasodilatation had occurred. Two other cats with large lesions placed more laterally in the tegmental region exhibited normal temperature regulation, except for an elevated threshold to panting in one.

The results at the level of the anterior midbrain indicate either that the correct distribution of lesions for destroying the heat-conservation pathways was not attained, or that these pathways are so widely distributed at this level as to be only partially affected by lesions of the size produced, for no evident impairment in heat conservation could be detected in any of the cases. An impairment in heat-loss activity, indicated by an elevated threshold for initiation and by a reduction in the total response, was greatest after the tegmental lesions in cat 4. In this case, some polypnea occurred but neither panting movements nor sweating were evoked on raising the body temperature to 106°. A similar tegmental distribution of heat-loss pathways was found at more caudal levels.

Lesions of the Caudal Midbrain

More pronounced impairment in temperature regulation followed lesions in the caudal midbrain.

Lateral region. Cat 5 with the large lateral lesions shown in Fig. 2A, though its temperature was normal in a warmer environment, ran subnormal temperatures of 96–97° when the room temperature was 71–72°, and on these occasions no piloerection could be observed but periods of shivering were noted. During 3 hours in an icebox, 3 weeks postoperatively, its temperature fell to 95° and though shivering was definite no clearcut piloerection could be observed. An even more pronounced deficit in heat-loss function was found. When the animal's temperature was elevated to 107° in a hotbox, the respiratory rate remained at 36 per min., and there was no panting or sweating.

Another animal, in which smaller lateral lesions destroyed the periphery of the brain stem with irregular softening extending into the tegmentum, exhibited a normal defense against cold. Three weeks postoperatively, the body temperature remained at 102.4° during 3 hours in an icebox, and good

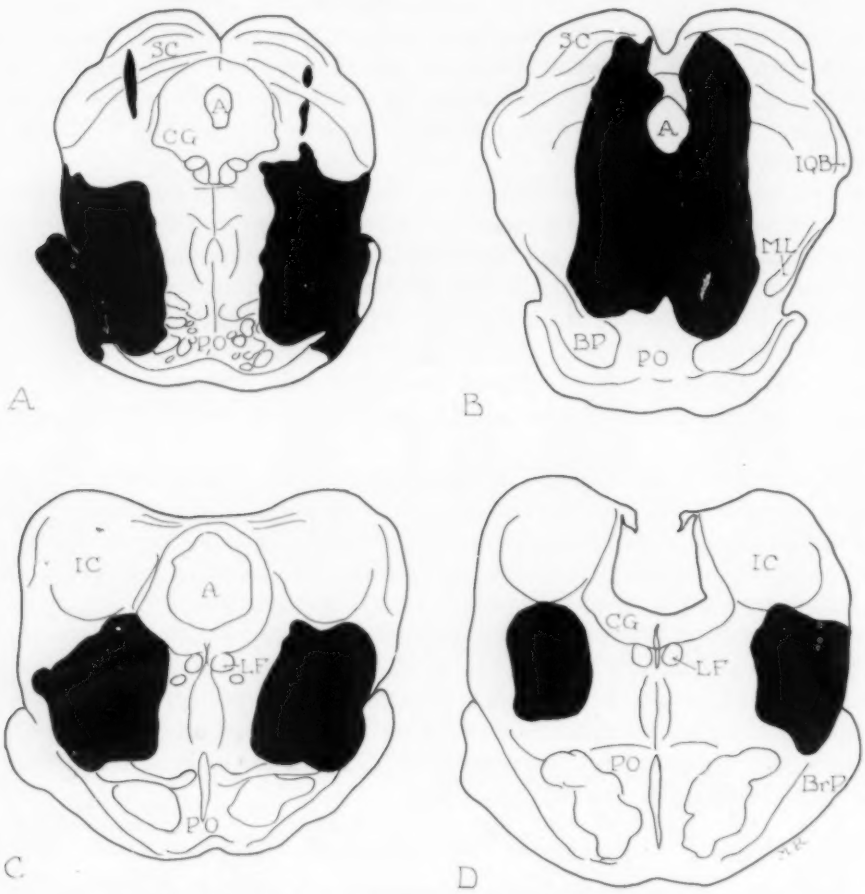

FIG. 2. A–D. Levels through the caudal midbrain showing the widest extent of the lesions in Cats 5–8, respectively.

piloerection and some shivering occurred. Elevating this animal's temperature to 107° in a hotbox resulted in slight sweating and a polypnea of 180 per min. with poor panting movements.

Medial region. Cat 6 with destruction of the entire medial part of the caudal midbrain (Fig. 2B), when tested 2 weeks postoperatively, exhibited a slight fall in body temperature to 99° during a 3 hour period in an icebox, but shivered violently and showed moderate piloerection in this situation. When its body temperature was elevated to 107° in a hotbox it sweated pro-

fusely on the footpads, but did not pant and the respiratory rate increased only from 42 to 66 per min. The next 2 cases indicate that the tegmental rather than the central extent of the injury in this animal was responsible for the heat-loss deficit.

Tegmental region. Cat 7 with bilateral tegmental lesions, sparing the central grey matter and the paramedian region below it (Fig. 2C), was tested 3 weeks postoperatively. During 3 hours in an icebox it showed a slight fall in body temperature from 101.8° to 100.8°. It shivered well but piloerection was only slight. When its temperature was elevated to 107° in a hotbox, the respiratory rate remained at 40 per min. and no panting or sweating occurred.

In cat 8, a smaller tegmental lesion (Fig. 2D) produced just as severe an impairment in heat-loss function. Three weeks postoperatively, when its body temperature was elevated to 107° in a hotbox, the respiratory rate was 42 per min. and there was no panting or sweating. During a 3 hour period in an icebox, its temperature fell from 102.8° to 100.3°, then rose and remained at 101°. It shivered markedly and showed intense piloerection. Smaller and slightly more medially placed lesions of the dorsal tegmentum in another animal were followed by normal temperature regulation except for a slight elevation in the threshold for panting.

The impairment of heat-loss function encountered after lesions of the caudal midbrain appears to be the result of interrupting tegmental pathways, for it was just as extreme following lesions confined to the tegmentum as in cases with injury to adjacent parts. The heat-loss pathways concerned appear to be more numerous in the intermediate tegmental region than in the paramedian part, for intermediately placed lesions (cat 7 and 8), sparing the paramedian region, caused even greater impairment than did more medial lesions which included it (cat 6). The two components of heat-loss activity, facio-respiratory alteration and sweating, would appear to be activated by distinct structural connections, rather than by collaterals from a single pathway, for the lesion in cat 6 dissociated the two; an elevation of body temperature in this animal resulted in profuse sweating but only questionable polypnea and no panting.

Similarly, heat-loss and heat-conservation activities may be dissociated by lesions at this level, as has previously been shown by Keller (2). Heat conservation was most markedly impaired after the laterally placed lesions in cat 5, suggesting a concentration of connections for this activity in the lateral part but not in the periphery of the caudal midbrain. This animal was still able to shiver, however, and maintained its body temperature nearer the normal level than do animals in which the heat-conservation mechanism is entirely destroyed at the hypothalamic level. It is clear, therefore, that the heat-conservation pathway is not confined to the lateral region, though seemingly better represented there than in the central region, the extensive destruction of which in cat 6 resulted in only a minor impairment in this function.

Lesions at the Pontile Level

The lesion in cat 9 interrupted all periventricular connections passing backward from the caudal end of the cerebral aqueduct, and extended asymmetrically into the deeper parts of the neuraxis (Fig. 3A). Four weeks after operation, the animal showed only a slight drop in body temperature from 101.4° to 100.6° during a 3 hour period in an icebox, and exhibited very good piloerection and fair shivering. When its temperature was elevated in

Fig. 3. A, B. Oblique sections at the pontile level showing the widest extent of the lesions in Cats 9 and 10.

a hotbox to 105.6°, it showed a polypnea of 174 per min. with a few panting movements when the mouth was opened, but no sweating occurred.

Cat 10 with lesions of the dorsolateral tegmentum shown in Fig. 3B, exhibited a slight fall in body temperature from 101.4° to 100.5° when tested for 3 hours in an icebox, 5 weeks postoperatively. Good piloerection occurred but there was no discernible shivering, though the animal shivered well in its preoperative test. When heated to 106° in a hotbox, the animal's respiratory rate increased to 96 per min., and slight sweating was seen on the right forepad, but no panting occurred.

At this as at more anterior levels, the impairment in heat-loss function appears the result of interrupting pathways concentrated in the intermediate or lateral part of the dorsal tegmentum. Interruption of periventricular connections in cat 9, did not impair heat-conservation activity sufficiently to cause any significant abnormality in the animal's regulation against cold. The dissociation in heat-conservation function encountered after the lateral lesions in cat 10, in which shivering was abolished while piloerection remained elicitible, suggests that the different heat-conservation activities, like the different heat-loss activities, are effected by distinct anatomical connections rather than by collaterals from a single pathway.

The presence of piloerection in response to cold, and also in response to the presence of dogs, in cat 9 and 10 must mean that the tegmental injury

in these cases was insufficient to interrupt the pilomotor pathway which Walker (5) has located at this level in the dorsolateral tegmentum adjacent to the brachium conjunctivum.

Summary

The brain stem pathways subserving temperature regulation in the cat have been investigated by examining the animal's regulation to a hot or cold environment, 2 to 5 weeks after producing bilateral lesions at anterior and caudal midbrain and at pontile levels.

Pathways subserving heat-loss functions appear to be concentrated in the intermediate and lateral part of the dorsal tegmentum at each of the levels studied.

Pathways subserving heat-conservation activities appear to display some concentration in the lateral as opposed to the central portion of the caudal midbrain and pons.

Following appropriately situated lesions, heat-loss activities were in some cases abolished while heat-conservation activities were maintained. This dissociation clearly indicated the existence of dual heat regulating mechanisms, whose efferent pathways are sufficiently independent to be destroyed separately.

In the case of both heat loss and heat conservation, the component autonomic and somatic activities, sweating and facio-respiratory alteration, and piloerection and shivering, have been observed to be dissociated following appropriate lesions. Apparently these different activities are mediated by distinct anatomical connections rather than by collaterals from single pathways.

In general the results present additional evidence for the greater importance of descending tegmental as compared with descending periventricular connections in efferent conduction from the hypothalamus.

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SPINAL DISTRIBUTION OF THERMOREGULATORY PATHWAYS IN THE MONKEY

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(Received for publication October 20, 1942)

STUDIES OF descending thermoregulatory pathways in man have indicated their predominantly ipsilateral distribution in the lateral and anterolateral columns of the spinal cord (1, 2, 3, 4). Tests of temperature regulation in each of 10 monkeys with lower brain stem or spinal cord lesions indicate a distribution of thermoregulatory pathways in the monkey in part like and in part different from that in man.

METHOD

In 2 animals (*Macaca mulatta*) the lower brain stem was hemisected at the pontile level. In 8 others unilateral lesions of the lateral or anterolateral column of the spinal cord were made at the cervical or thoracic level. The animals were prepared for other purposes but 2 to 6 weeks after operation, they were tested in an icebox at 32°F. or by confining their trunk and lower extremities in a hotbox at 122°F. In each case the extent of the lesion was verified at autopsy by microscopic examination.

RESULTS

In the 2 cases with hemisection at the pontile level, an unexpected dissociation was encountered in the distribution of pathv ys subserving the responses to heat and cold. On exposure to heat both monkeys sweated profusely on the side of hemisection, while sweating on the opposite side of the body was barely perceptible in one case and wholly absent in the second animal. These results indicate that little or no crossing in the descending sweat pathway occurs above the level of the pons, but between the pons and the thoraco-lumbar outflow this pathway undergoes a complete or almost complete decussation.

On exposure to cold, the 2 hemisected monkeys piloerected and shivered on both sides of the body. In each case, however, piloerection was more marked on the intact side. Shivering was more pronounced on this side in one case and appeared equal on the 2 sides in the second animal. After the animals were removed from the icebox, shivering and piloerection relaxed and disappeared first on the side of hemisection, at a time when they still remained marked on the intact side. These results indicate that the descending pathway for piloerection and shivering is both crossed and uncrossed, the uncrossed component being the greater.

In each of 4 monkeys with sections of the spinal cord destroying the lateral funiculus at C 4, except for varying amounts of its most ventral part, piloerection and shivering were present on exposure to cold and equal in degree on the 2 sides of the body. In a fifth case shivering was slightly reduced in the ipsilateral arm. The results do not rule out a minor representa-

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tion of pathways for shivering and piloerection in the lateral column, but do indicate that they are well represented elsewhere in the cord.

In each of these 5 monkeys with lateral column lesions at the cervical level, sweating on exposure to heat was equal on the 2 feet and in one it was equal on the 2 hands. In the other 4, sweating was impaired on the contralateral palm. In one animal this was indicated only by a delayed appearance of sweat on the contralateral palm, in the others sweating on the contralateral palm was significantly reduced. In 2 cases the contralateral palm was also less flushed than the ipsilateral. These results indicate a significant but not exclusive representation of sweat pathways in the lateral column of the cervical cord, those for the arm being better represented than those for the leg. A similar vasodilator representation is also suggested. The crossed distribution of sweating and flushing, analogous to that seen after hemisecting the lower brain stem, indicates that the decussation in the heat-loss pathway is a spinal one, that for the arm component being situated below C 4.

In each of 3 monkeys, sections interrupted the lateral column at thoracic levels below the preganglionic outflow to the upper extremities, and in 2 of the cases the adjacent portion of the anterior column was also injured. In the latter animals, an impairment in piloerection and shivering in the ipsilateral flank and leg was noted, suggesting the representation of pathways for responses to cold in the anterior rather than the lateral column of the spinal cord. In all 3 cases an impairment in sweating on the contralateral foot was evident, and in the monkey with greater injury to the anterior column, sweating was abolished on the contralateral foot while profuse on the ipsilateral. Sweat pathways for the lower extremity are evidently located in both the lateral and anterolateral columns of the thoracic cord and cross below the midthoracic level.

Summary

In the monkey, thermoregulatory pathways for sweatings are located in the lateral and anterolateral columns of the spinal cord and exert a completely or almost completely crossed influence. The crossing is a spinal one, located close to the level of preganglionic outflow.

Little evidence was encountered for the presence of pathways for piloerection and shivering in the lateral column of the spinal cord. These pathways appear to be situated in the anterior column, and are both crossed and uncrossed, the uncrossed component being the greater.

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THE RESPONSE OF SINGLE AUDITORY-NERVE FIBERS TO ACOUSTIC STIMULATION

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(Received for publication October 30, 1942)

THE AIM OF the experiments described here was to study the response of single auditory-nerve fibers to acoustic stimulation delivered to the intact ear. Similar studies on other single afferent fibers have remarkably extended knowledge of the mode of action of diverse sensory mechanisms, while at the same time emphasizing their fundamental similarities. The present report describes the behavior of single auditory fibers and stresses similarities to other sensory nerves; in a subsequent paper we hope to relate these findings to a specific theory of action of the mammalian cochlea.

METHOD

Young cats anesthetized with dial (0.75 cc. per kilo) were used in these experiments. The postero-dorsal aspect of the auditory nerve was exposed by removing the lateral portion of the occipital bone where it meets the petrous bone. Bleeding from the sinus petrosus inferior was stopped by judicious cauterization or by Clotting Globulin.*

A Ringer-filled glass micropipette with Ag-AgCl wire inserted as close as possible to the tip served as the active lead from the nerve. It was early established that pipettes with openings greater than 5μ do not allow isolation of the action potentials of single auditory fibers. The 3 to 5μ electrodes used have an impedance of about 1 megohm when tested on a resistance-capacity bridge between 0.6 and 2.5 kc. The microelectrode and the indifferent electrode (a silver plate in the neck muscles) led to a capacity-coupled amplifier (Grass) with an input impedance of about 8–10 megohms. Recording was done photographically from a cathode ray oscillograph. A neon bulb at the edge of the cathode-ray tube-face signalled the duration of presentation of sound.

Pure tones were ordinarily used as stimuli. A rubber hose conveyed the sound from a loudspeaker to the ear of the animal. The sound system differs in no important respect from that already described from this laboratory† (4). The tones were generated by a beat frequency oscillator having a range up to 40,000 c.p.s. (G.R. 713-B). Their intensity was controlled by an attenuator graduated in 2 db steps. Our reference level (0 db) is 2 V. output from the oscillator. This level corresponds to a sound intensity delivered to the ear of the animal of approximately 100 db above human threshold at 2000 cycles.

* We are indebted to the Lederle Laboratories for a generous supply of this effective hemostatic agent.

† For a complete description see J. E. Hawkins, Jr., "Electrophysiology of the Auditory Area of the Cerebral Cortex," a thesis on file at Widener Library, Cambridge, Mass.

Each experiment began with a determination of the threshold of aural microphonics for clicks and pure tones as recorded from the round window with a large silver-wire electrode. Animals shown by this test to be markedly less sensitive than normals almost invariably had suffered section of the cochlear blood vessels during the operation. If the round window responses were normal, the cochlear electrode was removed and the microelectrode introduced into the auditory nerve with a micromanipulator until large,

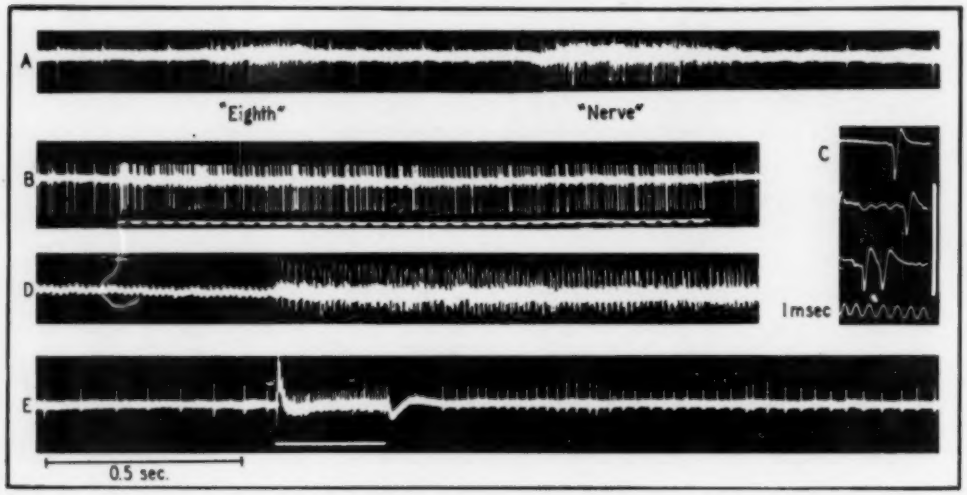

FIG. 1. Responses of single auditory-nerve fibers. In this and subsequent records a downward excursion indicates microelectrode negativity; the white line below a record marks duration of acoustic stimulation; and numbers in parenthesis indicate the characteristic frequency and minimal intensity for the fiber in question, reference level for intensity being 2 volts from oscillator. A, effect of the words "eighth nerve" upon the response of a fiber specifically sensitive to 2000 c.p.s. B, effect upon response of another fiber (17,100, −82 db) of a 17,100 c.p.s. tone at −60 db. C, high-speed sweeps of the fiber shown in B. Upper sweep, no sound on; lower two sweeps, response to 17,100 c.p.s., −60 db. The time line is an oscillogram of a 1000 c.p.s. tone. D, another fiber (7000 c.p.s., −90 db) responding to 7000 c.p.s., −68 db, in which no spontaneous activity like that shown in A and B occurred preceding onset of stimulus. E, example of the "silent period" and "after-discharge" following sound stimulation. This fiber (10,000 c.p.s., −84 db) was stimulated with 10,000 c.p.s., 0 db—a very intense tone.

simple, diphasic potentials registered on the tube face when a vocal sound (or a whistle or hiss) was made near the cat's ear. The experimenter then left the cat isolated in a quiet sound-deadened room, and presented subsequent sounds by remote control through the loudspeaker.

RESULTS

A. General. Figure 1 shows the type of response obtained from favorable preparations. In A, the words "eighth nerve" spoken in a conversational tone at a distance of about 20 feet from the cat elicited the response pictured. In B, acoustic stimulation caused an increase in rate of discharge of another isolated unit.

Evidence that the isolated unit is a single nerve fiber comes from the simplicity of the recorded electrical pattern (Fig. 1C). The records consistently show an initial negative spike followed by a positive phase, and the amplitude and duration of the discharge remain practically constant in spite of variation of frequency and intensity of stimulation over a period of many hours. In some records, it should be pointed out, the negative phase is reduced or absent (Fig. 9).

Further support for the conclusion that electrical records from single fibers are here under consideration comes from the difficulties experienced in setting up an adequate preparation. A smooth base-line broken by sharp

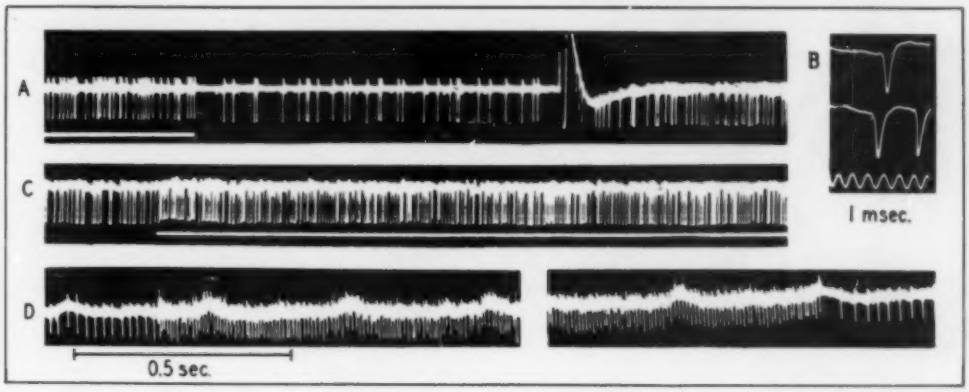

FIG. 2. Responses of single auditory-nerve fibers. A, B, and C, the same fiber pictured in Fig. 1, B and C (17,100 c.p.s., −82 db). A, diphasic responses become monophasic after the artefact, which marks turning off of the camera motor. B, sweeps of the monophasic response shown in A and C. Compare with Fig. 1C. The time line is an oscillogram of a 1000 c.p.s. tone. C, effect of 17,100 c.p.s., −68 db. D, another fiber (4000 c.p.s., −90 db) in which stimulus of 4000 c.p.s., −80 db causes increase of monophasic response. Note brief silent period at off.

spikes when the sound goes on is not commonly seen. Usually the electrode picks up numerous spikes of varying amplitude, giving a complicated picture obviously representing activity in many neural units. Subsequent careful adjustment of the microelectrode often enhances the response of one unit while diminishing that of the others, which become merely annoying fluctuations on the base-line. These manipulations, it should be noted, often increase or decrease the relative amplitude of the positive phase. This fact is difficult to reconcile with the known properties of the nerve discharge unless it be assumed that the geometrical relation between very small microelectrodes and the active tissue determines in some important way the electrical pattern which will be recorded.

On more than one occasion during the recording of single fiber potentials, the customary diphasic pattern suddenly changed to a monophasic negative discharge. The phenomenon usually occurred during manipulation of the electrode or following some activity by the experimenter which could have

jarred the preparation. The monophasic discharge had a high initial rate and relatively large amplitude. During the next few minutes both rate and amplitude progressively diminished until the discharge became lost in the random activity of the base-line.

The monophasic discharge just described has been interpreted as injury potential set up at the site of the electrode by its coming in contact with the fiber. The obliteration of the positive phase and increase in amplitude and duration of the negative phase, as well as the abrupt transition from diphasic

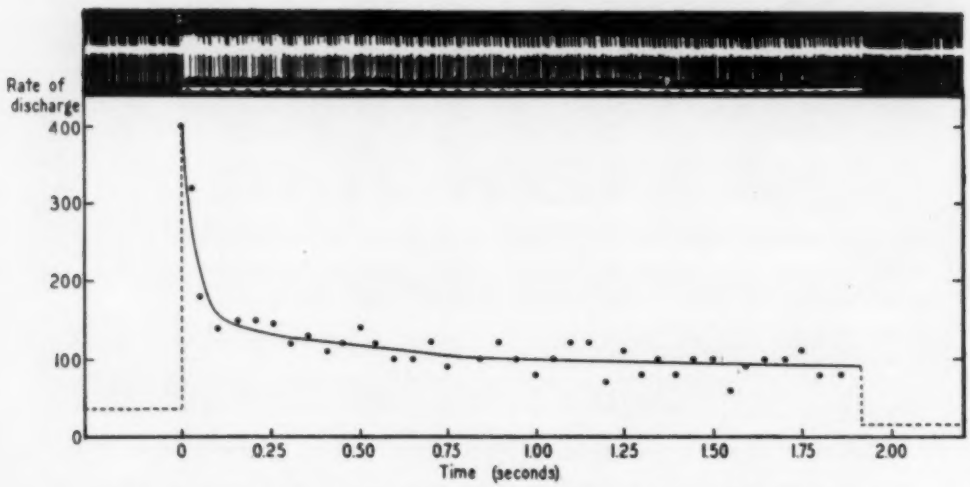

FIG. 3. Rate- and amplitude-adaptation by single auditory-nerve fiber (17,100 c.p.s., −82 db).

to monophasic discharge, support this interpretation. Figure 2 shows examples taken from the records.

Sound stimulation causes an increase in rate of monophasic discharge analogous to that described for the diphasic discharge (Fig. 2C, D). This probably means that even though the nerve is being excited by the contact of the electrode, with consequent passage of impulses toward the periphery, the end organ is still able to stimulate in the normal way. Such impulses as do arise, however, ascend only as far as the electrode.

The isolated auditory fiber may discharge in the absence of acoustic stimulation. Examples of this activity, which will be termed "spontaneous," are seen in Fig. 1A to C. More than half the fibers isolated reacted spontaneously; occasionally (Fig. 1D) one did not. Spontaneous activity appears to be common in sensory nerves (see 8, p. 572). In reading records from such fibers, excess discharge over the spontaneous rate may be taken as indicating response to the acoustic stimulation delivered by the experimenter.

A brief silent period during which spontaneous activity is absent often occurs upon cessation of stimulation (Fig. 1B, E). Following very intense

stimuli, the silent period may be succeeded by a period of marked acceleration of the spontaneous discharge (Fig. 1E).

B. Adaptation. A decrease in the voltage output of the auditory nerve shortly after onset of sound stimulation was noted and termed "equilibration" by Derbyshire and Davis (4). They attributed this phenomenon to (i) decrease in the rate of discharge and (ii) decrease in voltage output of each responding fiber. We shall refer to these two factors as rate-adaptation and amplitude-adaptation, respectively. Figure 3 shows that this explana-

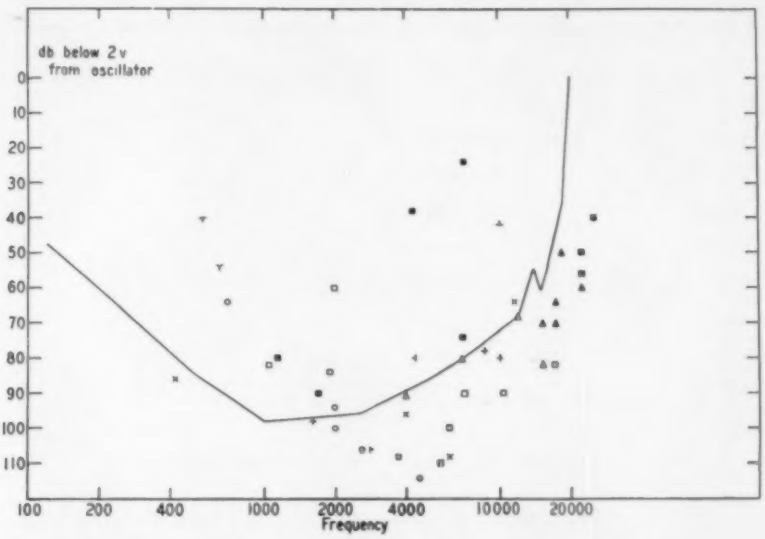

FIG. 4. Frequencies and intensities at which minimal responses were obtained from single auditory-nerve fibers. Each point marks the characteristic frequency and minimal intensity of one unit. Solid line shows aural microphonic thresholds for one of the cats used in these experiments (nerves isolated from this cat are indicated by the open squares). Each symbol represents a different animal.

tion, offered for data collected with a (large) co-axial electrode, is supported by the study of single fiber responses. The rate of nerve discharge at the onset of stimulation is relatively high, but drops off with time; this type of adaptation in auditory fibers is like that occurring in other sensory fibers (1, p. 23 ff.). Furthermore, a diminution of spike height (voltage) also takes place in accord with observations that rapid discharge prevents complete functional recovery of the nerve fiber (7). As a general rule, both rate- and amplitude-adaptation can be expected to be substantially complete within a few tenths of a second after a fiber begins to respond (see Fig. 1B, and 9). Some fibers, like that pictured in Fig. 7, appear not to exhibit the adaptation phenomena.

C. Minimal response of single fiber. Whether or not a single auditory-nerve fiber will respond to a pure tone depends upon both the frequency and

the intensity of the sound striking the ear. When intensity is fixed at a value just sufficient to cause minimal response, only a narrow band of sound frequencies excites a given auditory-nerve fiber. Thus we may assign to each fiber a characteristic frequency band and a particular minimal intensity, and refer to these as the "characteristic frequency" and the "minimal intensity" respectively. For example, a particular fiber increased its rate of discharge a just perceptible amount over the spontaneous rate (*i.e.*, it "began to respond") when sound frequencies near 2000 c.p.s. at an intensity level of

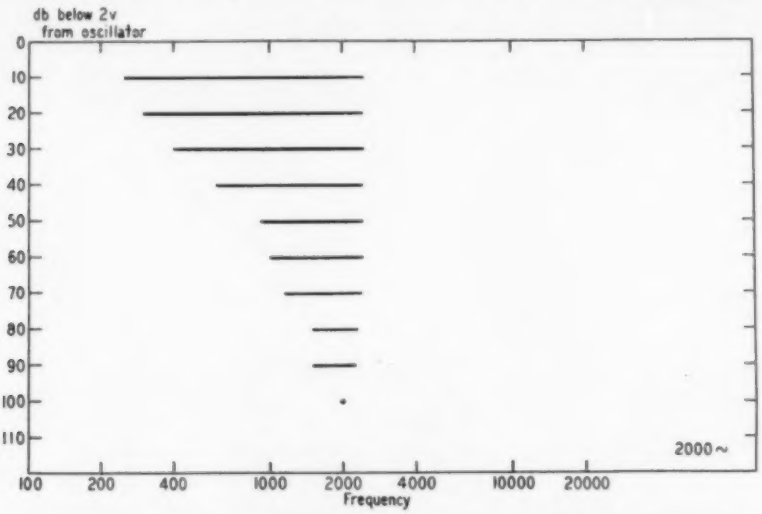

FIG. 5. Data used to construct the response area for an auditory fiber (2000 c.p.s., −100 db). At the intensity level given on the ordinate those frequencies covered by the horizontal line caused the fiber to respond. Note that as intensity increases (less attenuation) the range of stimulating frequencies is extended. The spread, however, is unsymmetrical.

100 db (below 2 V.) were presented to the ear. At 102 db, all frequencies were ineffective. This fiber, therefore, had a "characteristic frequency" of 2000 c.p.s. and a "minimal intensity" of −100db, and it may hereafter be designated as "the 2000 c.p.s., −100 db" fiber.

Figure 4 shows the characteristic frequency and minimal intensity values for some forty fibers. It will be noted that no fibers with characteristic frequency below 420 c.p.s. were isolated in spite of repeated attempts to find them. This may mean that the cat has no fibers specifically sensitive to frequencies below about 400 cycles, or that the standard operation used throughout this study does not favor their isolation.

How extensive is the range of frequencies which excite at minimal intensity? For a 700 cycle fiber the range was ±10 cycles, *i.e.*, between 690 and 710 c.p.s. For a 7000 cycle fiber it was ± about 100 c.p.s. Thus although in terms of cycles per second the bands are narrow for "low frequency" and broad for "high frequency" fibers, relatively they are about the same. Each

fiber may therefore be said to "tune in" sharply to a specific and narrow region of the sound spectrum. This finding is of first importance in establishing the mode of action of the cochlea in hearing.

On comparing minimum intensities required for activation of nerve fibers and for the appearance of aural microphonics (Fig. 4), two important points emerge. First, aural microphonic thresholds (measured at the round window) appear to be a poor index of the minimum sound intensity required for nerve stimulation. This is particularly true for high frequencies: while no cochlear potentials above 20 kc. can ordinarily be measured at the round

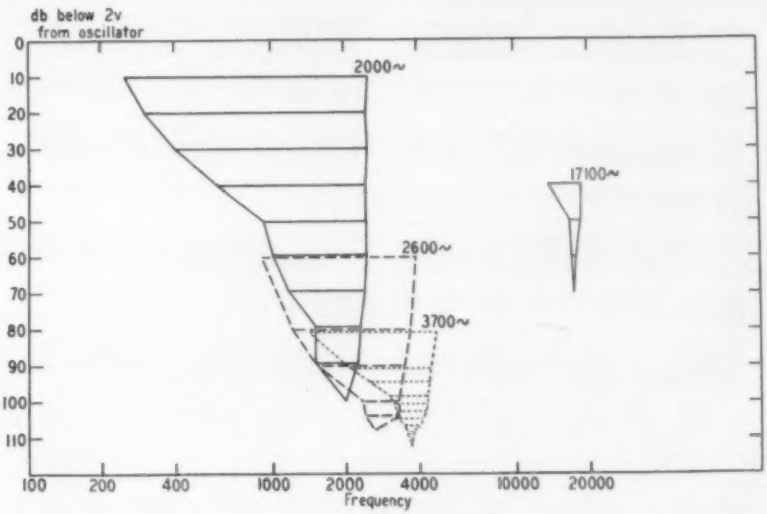

FIG. 6. Response areas for 4 different fibers. The 3 at the left of the figure are from the same animal. The 2000 c.p.s. response area shown here is the same one pictured in Fig. 5.

window, yet nerve fibers excited by greatly attenuated sounds of frequencies of 25 kc. or higher are found with relative ease. It is also important that although over the 1 to 10 kc. range the minimal intensity for some fibers lies near the threshold of the aural microphonic, other fibers may require for excitation much reduced, or much increased, intensity. This indicates that there are many nerve fibers which respond to a given frequency, and that they are called in successively as the sound intensity is raised.

The range of sound frequencies capable of exciting a fiber becomes more extensive as the intensity level is raised. This fact is shown in Fig. 5. At each value given on the ordinate (intensity level), those frequencies covered by the solid horizontal line were able to excite. The sharp tuning noted at the minimal intensity obviously disappears as intensity level is raised. At 90 db above its minimal intensity, this particular fiber is excited by all frequencies between 250 c.p.s. and 2500 c.p.s., representing, respectively, 3 octaves below, and only about $\frac{1}{2}$ octave above the characteristic frequency. These

facts will be considered in detail later as evidence that larger and larger areas of the basilar membrane respond to increasingly more intense tones.

A line connecting the ends of the frequency bands shown in Fig. 5 encloses a roughly triangular area which contains each sound frequency and intensity capable of stimulating the given fiber. This area may be termed the "response area" for that nerve fiber, and each response area is unique. Figure 6 shows response areas for three fibers from one animal; where over-

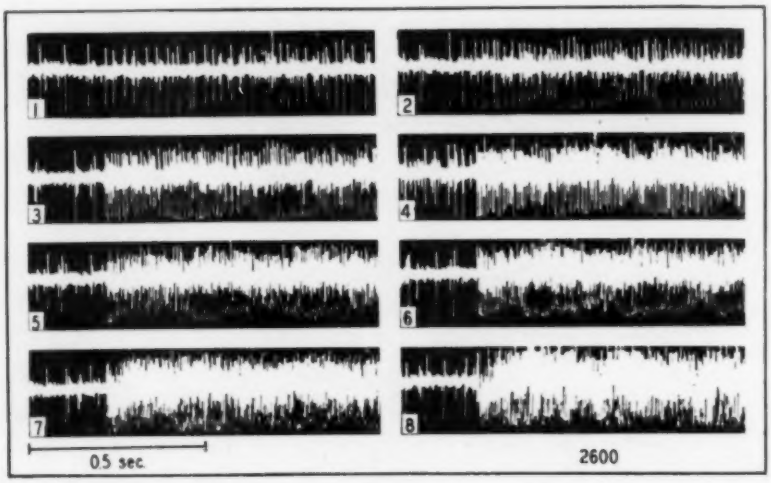

FIG. 7. Frequency of nerve discharge as a function of sound intensity. This fiber (2600 c.p.s., −110 db) behaves toward increase in intensity by increasing its rate of discharge. Intensity level at which above records were taken (in db): 1, −110; 2, −106; 3, −102; 4, −98; 5, −94; 6, −90, 7, −80; 8, −60. The gradual coarsening of the baseline as intensity is increased probably means that the microelectrode, although singling out one fiber fairly clearly, was picking up the responses of many fibers in the same tract.

lapping occurs, stimuli are defined which would have excited both (or all three) fibers.

The continuous "V"-shaped line which marks the lower boundary of each response area in Fig. 6 may be thought of as the threshold curve for excitation of the corresponding fiber. This threshold excitation curve gives the intensity required to elicit a just perceptible increase in nervous activity at each frequency.

D. Response of the single fiber as a function of sound intensity. The rate of discharge of an isolated auditory fiber is determined by the frequency, the intensity, and the time after onset of the stimulating tone. How the fiber "equilibrates" or adapts with time has already been demonstrated (Fig. 3), and how rate of discharge depends, at constant intensity, on sound frequency will be treated under "iso-intensity contours" (see below); this section will

describe the very considerable part played by sound intensity in determining nerve discharge rate.

"Minimal intensity" has been defined as that intensity level which just causes discharge, or, if the fiber is spontaneously active, where a just perceptible increase over the spontaneous rate occurs. When stimulus intensity is raised above the minimal the fiber responds by discharging more rapidly. Figure 7 illustrates this fact; in Fig. 8 data from three different fibers are

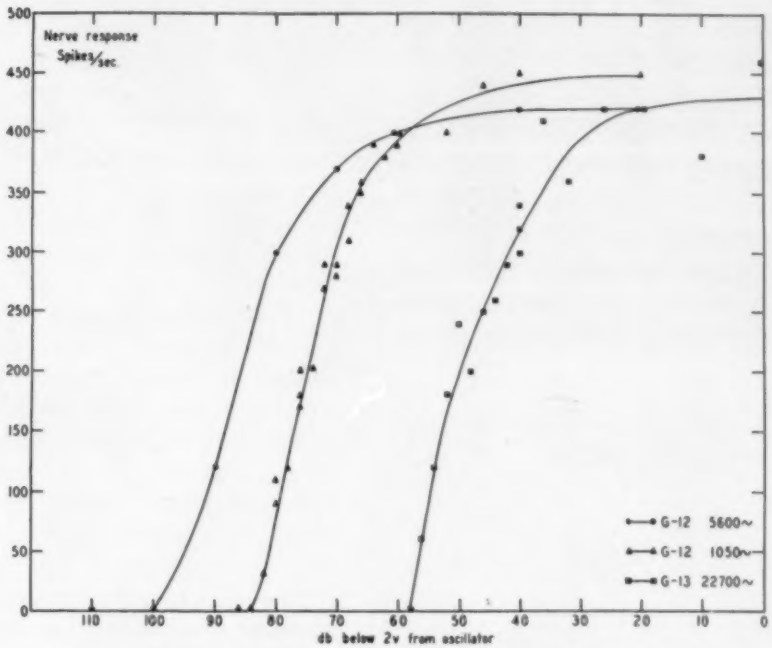

FIG. 8. Graph showing increase of nerve discharge rate with increase of sound intensity for 3 different fibers. Points determined from records like those in Fig. 7 by counting spikes occurring during first 0.1 sec. and multiplying by 10.

plotted. Frequency of nerve discharge (spikes per second) clearly varies with stimulus intensity for auditory fibers as for other sensory fibers. For most auditory fibers the maximum discharge rate is attained at sound intensities about 30 db above the minimal intensity.

The values of discharge rate plotted in Fig. 8 were calculated by multiplying by ten the spikes appearing in the first one-tenth second after onset of the tone. Reading the records in this way gives data on the maximum rate of discharge—on fibers undergoing rapid adaptation. When, instead of this, the total number of nerve discharges in the first second are counted and plotted, the resulting curves are like Fig. 8, except that lower values appear at each intensity and a maximum of 300 to 350 discharges per second is obtained with highest intensities. Typically, therefore, both the unadapted and the

partially adapted auditory fiber respond to increase in stimulus intensity by an increase in rate of discharge. About 400 discharges per second is the maximum rate, and a rapidly adapting fiber attains this rate when intensity is about 30 db above its minimal.

Exceptions to the above generalization are occasionally found. One fiber (1150 c.p.s., −80 db) discharged at a constant, slow rate (about 20 per sec.) regardless of stimulus intensity. Others, like that shown in Fig. 9 (10,000 c.p.s., −120 db) displayed marked reluctance to increase rate and never approached a maximum of 300 discharges per second. Results of this sort constitute a small percentage of the data and may eventually require special consideration and classification.

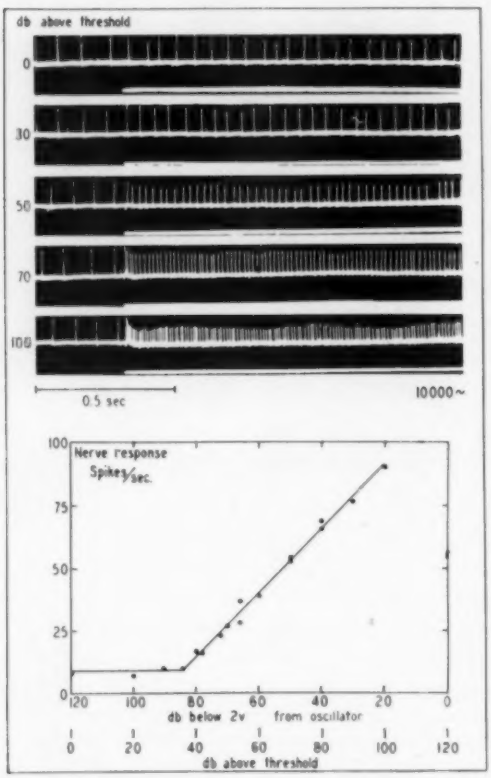

FIG. 9. Frequency of nerve discharge as a function of sound intensity. This atypical fiber (10,000 c.p.s., −120 db) not only had an extremely low minimal intensity but also reacted toward intensity increase by a linear increase in rate of discharge.

The behavior of the completely adapted single fiber to change in intensity is similar to what has just been described for unadapted or partially adapted fibers. Figure 10 shows segments from the continuous record of the response of a 2600 cycle fiber (the same one shown in Fig. 7) to a 2600 cycle tone; between each segment of the record, the intensity was raised 2 db. Figure 10 and the accompanying graph demonstrate that increase in intensity is followed by a higher rate of nerve discharge in an adapted auditory fiber. The maximum rate achieved, about 200 discharges per second, lies well below the unadapted maximum of 450 spikes per second.

Some adapted fibers do not behave in precisely the manner just described. One fiber, subjected to the procedure used for obtaining the data summarized in Fig. 10, maintained its equilibrated discharge rate of 50 to 60 responses per second in spite of an intensity increase of 50 db. No immediate explanation for this phenomenon is apparent.

E. Iso-intensity contours for a single fiber. The rate of discharge of a single auditory fiber was shown to depend, at constant sound frequency, upon intensity of stimulus. The question now arises as to how the fiber behaves when intensity is kept constant but frequency is changed.

This question was attacked experimentally as follows. Once the response area pictured in Fig. 5 was determined for a given fiber, records of nerve activity were photographed at appropriate frequencies for each intensity

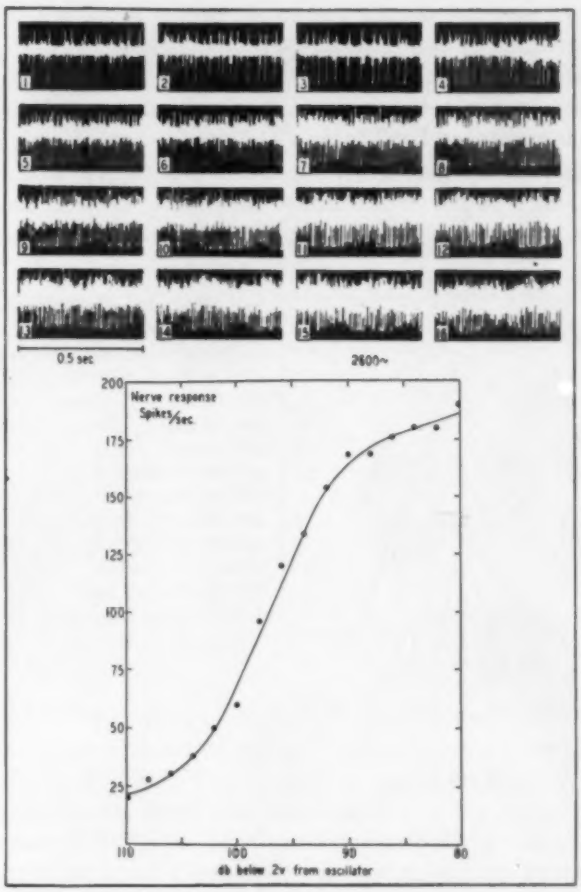

FIG. 10. Frequency of nerve discharge as a function of sound intensity for an adapted fiber (2600 c.p.s., −110 db). A 2600 c.p.s. tone was delivered continuously to the animal while the intensity was raised in 2 db steps. The successively numbered segments of record in the figure represent the adapted response of the fiber to 2600 c.p.s. as intensity successively changes from −110 db to −80 db in 2 db steps. Points on the graph were established by counting the number of spikes appearing in 1 sec.

level and the spikes appearing in the first second counted. Figure 11 shows the results for one such experiment. Each contour line relates rate of nerve discharge and sound frequencies at a fixed intensity level. The whole family of curves so obtained may be termed the "iso-intensity contours" for the

given fiber. Such contours show clearly that frequency of nerve discharge is not solely determined by stimulus frequency. Instead, nerve-discharge rate is a function of both the frequency and the intensity of the stimulus. To be sure, the sound frequency which first excites (in this case 7000 c.p.s.) is the most effective at any intensity, yet as intensity level is raised, activity is caused by frequencies at some distance from (and particularly those below) the characteristic frequency.

F. Phase relationship between nerve discharge and aural microphonic. Volley theories, as formulated by Troland (17, p. 44) and Wever and Bray (19), postulate a close relationship between sound frequency and nerve-discharge rate. The frequency of nerve discharge according to that theory should be either equal to, or some sub-multiple of, the sound frequency. A study of

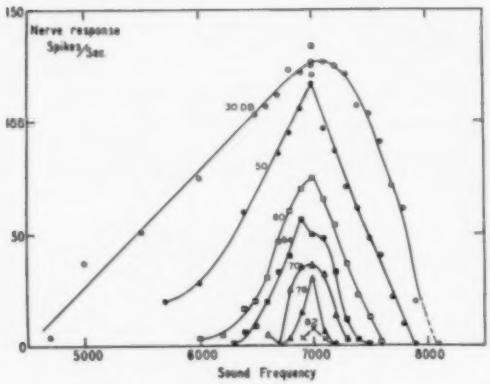

FIG. 11. Iso-intensity contours for a single fiber (7000 c.p.s., −84 db). The way in which frequency of nerve discharge varies with sound frequency is plotted here. The number on each contour line indicates the intensity level at which the determinations were made. This figure shows that as sound intensity level increases (numbers on contour lines get smaller), 1) the fiber is excited by frequencies which lie farther away; and 2) any frequency capable of exciting the fiber elicits more discharges. Frequency of nerve response is determined by both the frequency and the intensity of the sound stimulus.

Fig. 8, however, makes it appear that any frequency of nerve discharge (up to about 450 per sec.) may accompany any sound frequency, while a cursory glance at records such as those in Fig. 1 and 3 may lead to the conclusion that the nerve discharges in a haphazard and erratic manner. Such behavior if demonstrated, would be inconsistent with a volley theory, and we were therefore interested in designing an experiment to show whether the nerve impulse is synchronized with some phase of the sound wave.

To test whether the nerve discharge occurs at a particular and specific point in the sound wave cycle, both nerve response and aural microphonic were photographed simultaneously. This was made possible since under certain conditions the potential led off by the microelectrode included a significant component from the cochlea (aural microphonic) in addition to the nerve response. Although this meant introduction of an undesirable artifact into most of the records, it supplied exactly the conditions for relating nerve response to the phase of the sound stimulus.

In Fig. 12A responses of a single fiber are seen to clump closely about one half or less of each aural microphonic cycle. The aural microphonic in this record may be taken to represent the sound wave, and since the nerve spike shows a consistent phase relationship to the aural microphonic, this indi-

cates a similar phase relationship to the sound wave. The hundreds of sound wave cycles (measured, as just indicated, in terms of microphonic cycles) recorded in the sweeps in Fig. 12A gave rise to only tens of nerve discharges, yet it is perfectly clear that nerve impulses, when they do arise, consistently occur at a specific and particular portion of the sound wave cycle. Figure 12B shows the similar behavior of another fiber. Figure 13 illustrates the same point, and supplies the additional information that the nerve discharge is in synchronism with any sound wave of sufficient intensity to stimulate. These results both confirm and extend to volley hypothesis.

It will be noted that there is some variability in the spot on the aural

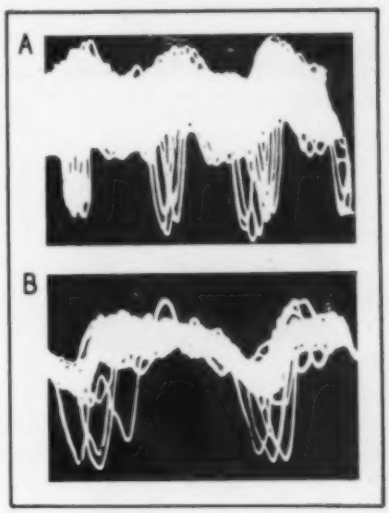

FIG. 12. Simultaneous recording of aural microphonic and single fiber response. Each record is the photograph of many sweeps on the cathode ray tube face. The responses of the nerve are the sharp downward deflections; aural microphonic is the undulating heavy line. A, 1050 c.p.s., −16 db delivered to the ear (minimal response from the fiber at 1050 c.p.s., −32 db). B, 550 c.p.s., −24 db delivered to the ear (minimal response at 550 c.p.s., −40 db). Records photographically intensified but not retouched.

microphonic cycle where the nerve impulse arises. The maximum variability amounts to about 0.25 msec. in Fig. 12A. If it be assumed that a similar variability occurs at other frequencies, it would be expected that the auditory nerve as a whole could not discharge synchronously above about 4000 c.p.s. This is the value arrived at experimentally by Wever and Bray (18) and by Derbyshire and Davis (4).

DISCUSSION

A. The behavior of auditory nerve fibers

1. Sensitivity. The threshold for excitation of a given auditory-nerve fiber is given by the series of points which marks the boundary of the response area (Fig. 5 and 6). Each point on this contour designates a tone which is just adequate for exciting the fiber. The point at which this contour passes through a minimum of intensity gives the "characteristic frequency" and "minimal intensity."

There is a resemblance between the contour showing the threshold for

activity in a single auditory unit and the familiar threshold of hearing curve. Both are defined in terms of the frequency and the intensity of the tone striking the ear and they both pass through a minimum. The principal difference lies in the relative narrowness of the frequency range for the single fiber.

The absolute sensitivity of auditory units apparently varies over a wide range (Fig. 4). The more sensitive units are just excited, at their characteristic frequencies, by intensities which must lie close to the absolute threshold of hearing. The less sensitive units, however, require for excitation intensities which must be "loud" to the cat.

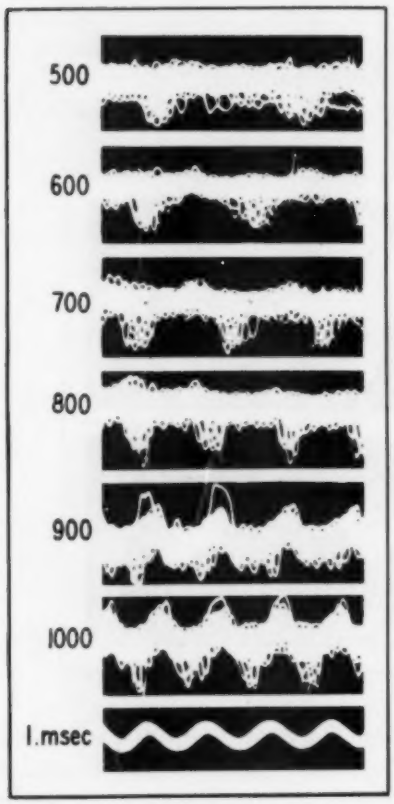

Fig. 13. Simultaneous recording of aural microphonic and single fiber response at different frequencies. This fiber (650 c.p.s., −52 db) discharges in phase with the microphonic at frequencies between 500 and 1000 c.p.s.

Regardless of whether the unit is sensitive or not, however, an increase in intensity of 2 db over the minimal intensity causes it to discharge, on the average, about 40 additional times each second (see Fig. 8). This is a very noticeable change in the response of the unit. It amounts to about 10 per cent of the maximum possible change.

It is interesting to compare this differential intensity sensitivity of the isolated auditory unit with that of the ear as a whole. The difference limen for intensity is usually given as about 3 db between 1000 and 4000 cycles at 5 db above threshold for human subjects (16, p. 138). The 3 db increase of intensity required to elicit a sensation of increased loudness (human) will cause about 50 additional discharges per second to arise in one auditory fiber (cat).

2. Spontaneous discharge, silent period and after-discharge. Spontaneous activity in sensory nerves appears to be a fairly common phenomenon. Thus many visual (8), olfactory (3), gustatory (15), lateral line (9), and now auditory afferents are known to discharge in the absence of any apparent stimulus. On the other hand, vestibular (12), touch (1, 5), visceral (10), vibratory (14) and striated muscle (13) afferents seem to display little if any spontaneous activity. Spontaneous activity appears to occur only when the nerve is in continuity with an active end organ. Lateral-line afferents cease discharging if cut peripheral to the recording electrodes (9). Adrian and Ludwig (3) showed that whereas spontaneous discharge in the nerve was reduced by anesthetizing

the end organ (olfactory bulb in fish), it could be abolished only by section of the nerve between the end organ and the recording electrodes. It is difficult to say exactly what constituted the olfactory stimulus in the above case, and indeed to determine whether there actually was one; the same difficulties arise in the case of the eye, tongue and ear. Two alternatives are apparent: either it is not possible completely to eliminate stimulus energy under even the best experimental conditions (*i.e.*, there is no such thing as a "stimulus-vacuum"), or a certain number of end-organ elements, always delicately poised at the brink of discharging, occasionally do so even though no stimulation of the sort usually considered adequate is presented. As an example of the latter alternative, slight mechanical movements induced by blood flow might be responsible for all spontaneous discharge. If this were true, it would appear that the cells of a given end organ, irritable to an extraordinary degree to one type of energy, nevertheless can be discharged by other types of stimuli.

In the case of the ear, spontaneous nerve activity may be due to discharge of the end organ stimulated by the many sounds which must constantly bombard the ear. Sounds attending respiration, heart beat and flow of blood through cochlear structures as well as those external noises resulting from inability to soundproof the experimental room completely may all constitute adequate stimuli for the sensitive end-organ structures.

The silent period is that fraction of a second following cessation of stimulation during which no spontaneous activity is detectable. The silent period was observed in most fibers isolated and seemed to be particularly marked after stimulation at high intensity levels; no attempt was made to study this phenomenon in any systematic way. A marked increase in spontaneous activity followed the silent period in certain cases where stimulation was very intense (Fig. 1E). Because of analogies to behavior of other end organs, this may be termed an after-discharge. It deserves further study since it may be correlated with the tinnitus which many persons experience after exposure to loud sounds.

3. Adaptation. Like certain visual, muscle spindle and pressure afferents, auditory nerves respond to a continued stimulus of constant intensity by a burst of impulses which gradually declines in rate. In this respect they clearly resemble the pressure sense organs from which they are embryologically derived.

The final rate of discharge maintained by an auditory receptor adapted with tones at ordinary intensity levels is 100 to 200 discharges per second, and the steady state is arrived at within a second or two. No further significant change occurs even though activity is recorded for as long as 30 seconds. The so-called "slow equilibration" discussed by Derbyshire and Davis (4) was not investigated.

The "rapid equilibration" of Derbyshire and Davis appears to result from a combination of rate- and amplitude-adaptation occurring in the fibers excited by the stimulus. Adaptation in amplitude of response may account

at most for 10 per cent of the total voltage drop undergone during equilibration, while rate-adaptation probably accounts for the remainder. Ordinarily the rate drops to 25 per cent of the maximum within a second after onset of stimulation, and some fibers, especially those not maximally excited by the tone, may adapt to extinction. Although it is difficult to assess the importance of rate-adaptation in rapid equilibration with any exactness, it seems clear that it may decrease the potential output of the auditory nerve to 25 per cent of its maximum within a second or so after the sound goes on.

4. Maximum rate of discharge. The maximum rate of nerve discharge appears to be determined not by the ability of the fiber to respond but by the capacity of the end organ to discharge. During the first 0.05 sec. after onset of stimulation, a series of impulses at a maximum rate not exceeding 500 per sec. may arise, yet one impulse can follow another at rates up to 900 or 1000 per sec. This seems to show that the nerve is only occasionally called upon to discharge at its highest rate.

The bottom sweep in Fig. 1C was reproduced to show the shortest interval between two impulses noted in some 500 high-speed records. The interval is about 1 msec. Intervals shorter than this—indicating rates higher than 1000 per second—have not been observed in hundreds of slow-speed records either; there is no justification for assuming, therefore, that auditory nerves display unusually brief refractory period phenomena.

B. Single fiber responses and hearing

1. General considerations. It is necessary to establish one point regarding the distribution of the peripheral endings of the auditory nerve in order to apply the data from single fibers to a specific theory of action of the mammalian cochlea in hearing. The question is simply this: are the endings of each fiber in contact with few or with many hair-cells? Lorente de Nó (11) discussed this problem and described five types of fibers, of which "radial" fibers end on a few neighboring internal hair-cells, while "spiral external" fibers end on hair-cells over a third of a turn or longer. The distributions of only two out of five fiber-types are known, and thus the question of how many hair-cells are capable of exciting a given nerve fiber receives only a partial answer from the excellent work of the anatomists.

Pending clarification of this problem, it will be assumed that each nerve fiber is in contact with a "small number" of hair-cells. From this assumption it follows that response in a single auditory fiber means excitation in a particular and restricted region of the cochlea. It will be noted that distortion of hair-cells resulting from movement of the basilar membrane is taken for granted as a prerequisite for nerve excitation. This train of events appears to be generally accepted as a fundamental part of the mechanism of hearing and needs no further discussion.

2. Pitch discrimination near threshold. In Fig. 4 the frequency and intensity at which minimal response was obtained from some 40 separate auditory fibers are plotted. At minimal intensity, each fiber responds to

only a narrow band of frequencies. All other frequencies are ineffective. This clearly indicates that each pure tone singles out and causes to move one particular and restricted region of the basilar membrane. For perception of pitch at threshold, then, the data from these experiments confirms a place theory of hearing, a theory according to which different regions along the length of the basilar membrane are excited by different sound frequencies.

3. Loudness. The principal psychological correlate of the intensity of a tone is its loudness. Our experiments show that an increase in sound intensity results in an increase in number of nerve impulses ascending the auditory nerve.

Increase in intensity of the sound stimulus excites more nerve activity in two ways. First, each active fiber discharges at a higher rate (see Fig. 8). Second, a larger number of fibers are made active. This is shown by Fig. 5 and 6 (response areas), where a given spot on the basilar membrane—fixed by the single fiber being studied—is excited by sound frequencies which lie farther and farther removed as the intensity level is raised. These response areas, demonstrated experimentally, can only be interpreted as supporting the familiar concept of spread of excitation along the basilar membrane as a basic explanation for loudness perception.

4. Pitch perception at high intensities. For man at least, a 2000 cycle tone near threshold has just about the same pitch as a 2000 cycle tone at a sensation level of 100 db. Our experiments show the involvement of a large basilar membrane area, with many nerve fibers excited, when the tone is loud, as opposed to a small area with few fibers excited at or near threshold intensity (Fig. 5, 6, and 11).

However, the ability of the frequency which first excites to continue, as intensity level rises, as the most effective stimulus is a consistent finding. Thus, in Fig. 11 where the iso-intensity contours for a 7000 cycle fiber are plotted, each 7000 cycle tone calls out more nerve activity at a given intensity level than any other stimulating frequency. This particular 7000 cycle fiber was always most readily excited by a 7000 cycle tone at any intensity level up to 50 db above its minimal intensity. At intensities above this, adjacent frequencies begin to cause maximal discharge, and consequently maximal discharge from this fiber can no longer serve as a clue for pitch. However, it should be recalled that a number of fibers have the same characteristic frequency but widely different minimal intensities. (See Fig. 4 at 7000 cycles.) The characteristic frequency is the most effective stimulus, therefore, to that intensity where all fibers "tuned" to that frequency have not yet been forced to respond at their maximum rate. This, in effect, is a restatement of Gray's theory of maximum stimulation.

In addition to causing maximum excitation at one spot on the basilar membrane, increasingly more intense tones at a given frequency appear to enlarge the area involved in a regular and systematic manner. This is shown both by the response-area evidence already discussed, and by the iso-intensity contours. It must be clear that the single fiber technique does not

allow direct exploration of the total area a given tone involves. Instead, it identifies only those tones which affect the area isolated. The evidence is nevertheless unequivocal for a gradual and systematic extension of the pattern of vibration of the basilar membrane as intensity is raised.

Here, then, is a second phenomenon common to all tones having the same pitch. They all cover the same minimum area; and the louder ones, while extending that minimum area in all directions, do so according to a series of regular rules. So long as the site of maximum stimulation remains fixed and new increments of area around the edges of that previously in vibration are added in a systematic way, the pitch stays constant.

It should be apparent that the discussion in this section very closely resembles the space-time pattern theory formulated by Fletcher (6). Similarities and differences will receive more complete attention in a later paper, in which, also, the pattern of vibration of the basilar membrane as derived from response-area data will be discussed.

Summary

The activity in single fibers of the auditory nerve in cats has been studied with the aid of microelectrodes. The fibers were excited by delivering acoustic stimulation to the ear. Each auditory-nerve fiber responds only to a narrow band of sound frequencies when the sound intensity is just sufficient to excite it at all. Fibers were found which were specifically sensitive to narrow bands of frequencies in the frequency range between 420 c.p.s. and 25,000 c.p.s. (Fig. 4).

The auditory fiber exhibits no unusually brief refractory phenomena. It may discharge spontaneously in the absence of any apparent sound stimulus. After a period of marked activity during sound stimulation, the spontaneous activity may be temporarily depressed (silent period), then accelerated (after-discharge) (Fig. 1).

The auditory fiber typically responds to a continuous adequate sound stimulus by a train of impulses initially high, but gradually declining in rate (Fig. 3). Within a few tenths of a second after the tone goes on this rate-adaptation is complete and the amplitude of the action potentials is somewhat diminished as well. It is concluded that auditory fibers behave in every important respect like other sensory fibers.

At constant frequency an increase in sound intensity causes an increase in rate of discharge by the single fiber (Fig. 8). Most fibers reach a maximum of 450 discharges per second after an intensity increase of about 30 db.

The frequency band capable of exciting a given fiber increases markedly as the intensity level is raised (Fig. 5). At levels about 100 db above threshold tones as far away as 3 octaves below and ½ octave above may be adequate.

The auditory-nerve fiber discharges in synchronism with a definite part of the stimulating sound-wave cycle (Fig. 12).

The results are held to support a place theory of hearing according to

which pitch is a function of where, and loudness a function of how much of, the basilar membrane is disturbed.

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A SECONDARY ACOUSTIC AREA IN THE CEREBRAL CORTEX OF THE CAT

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(Received for publication November 23, 1942)

PRESENT knowledge of the type of cortical association area known as parareceptive cortex (*e.g.* peristriate and parastriate areas) is based principally on cytoarchitectonic studies purporting to demonstrate that such regions of specific histological structure are related to associative functions. In addition, there have been several reports of the distribution of fibers from primary receptive zones to surrounding cortex, based on Marchi studies following experimental lesions in the primary areas. There is a division of opinion arising from these studies concerning the distance traversed by and pattern of distribution of such association fibers. In some instances bundles of fibers have been described which run for long distances to terminate in remote parts of the cortex. In others, there seems to be reason to believe that the frequently described long association bundles are improbable and that transcortical conduction is accomplished by fibers running only short distances. Presumably these are arranged in some sort of chain or network in such a way that impulses taking origin in a given locus may ultimately reach remote cortical loci. This hypothesis is difficult to correlate with the observation of several investigators that stimulation of a cortical locus may result in an electrical response in some other specific cortical locus, both loci being surrounded by great areas of non-responsive cortex.

The present communication is a report of experiments using the strychnine method on the temporal cortex of the cat; they grew out of and were incidental to the oscillographic mapping of the acoustic projection area. While the idea that strychnine may act upon cortical (or other) synapses in such a way as to facilitate synaptic transmission is not new, the application of this principal to a study of transcortical conduction pathways has been rather limited.

PROCEDURE

One or both hemispheres of the cat were exposed under deep Nembutal anesthesia. The areas of cortex showing responses to click stimulation were then mapped by the method described by Ades (1). Cortical response to sharp mechanical clicks delivered one foot (30 cm.) from the cat's ear was measured by means of a single-phase, capacity-coupled amplifier recording on a cathode-ray oscillograph. The active electrode was a saline-moistened thread drawn through a hypodermic needle and anchored to the skull by a holder permitting movement in any direction; the animal was grounded through a clip-lead attached to skin or muscle. The electrode, in light contact with the pia mater, was moved systematically in 2 mm. steps over an area sufficiently large to permit exact defini-

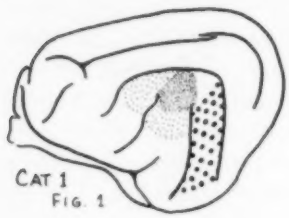
* Communication No. 53 from the Physiological Psychology Laboratory, University of Rochester (Elmer A. Culler, Director). This laboratory is maintained by aid of the Research Council, American Otological Society.

tion of the boundaries of the responsive cortex. Further explorations were made in similar fashion over wide cortical areas bordering the acoustically responsive area so defined.

The primary responsive area was next strychninized by applying to it a small piece of blotting paper moistened in a 1 per cent aqueous solution of strychnine sulfate. The previous explorations were repeated and other procedures were carried out as detailed below.

Results and Discussion

Ten cats were used. In all cases after strychninization of the primary responsive area, responses resembling the diphasic primary projection response occurred in a second, hitherto silent, region of the posterior ectosylvian gyrus. (See Fig. 1 and 2.) Usually there was a non-responsive area



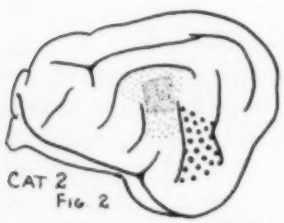
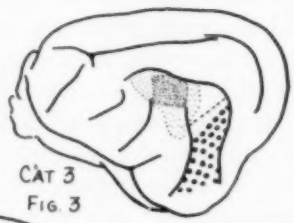
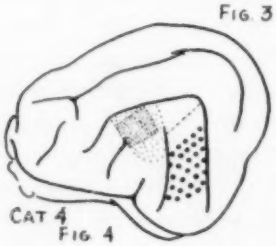


FIG. 1 and 2. Lightly stippled area on middle ecto sylvian gyrus shows primary projection area; heavily stippled portion within primary projection area indicates extent of strychninized cortex. Secondary responsive area is shown by heavy dots.





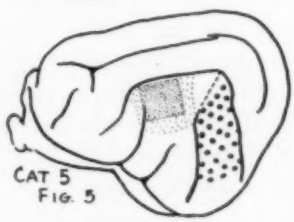


FIG. 3, 4, 5. Same symbols as Fig. 1 and 2. Broken line indicates position of incision made in cortex.

separating it from the primary area. In all cases, whether or not the two areas were contiguous, maximal secondary potentials were obtained from the upper part of the lower half of the posterior ectosylvian gyrus, and the magnitude of response diminished from that center in both superior and inferior directions. In no case was there a secondary responsive area anywhere except on the posterior ectosylvian gyrus.

The potentials from the secondary area could always be diminished by making a shallow (2 mm.) cut in the cortex across the posterior ectosylvian gyrus at the line or strip of demarcation between primary and secondary areas. (See Fig. 3, 4, and 5.) They could sometimes be entirely abolished by deepening the incision to 4 mm. In three cats, after determining the extent of the secondary responsive area, the primary area was decorticated by suction pipette. In each case, after such decortication, no vestige of response remained in the still intact posterior ectosylvian cortex.

The most obvious explanation of an area such as this, is that it constitutes a parareceptive zone, or acoustic association area. From the evidence adduced, one would expect to find strong fiber connections from middle ectosylvian cortex (primary acoustic area) to the posterior ectosylsylvian region of secondary response. One might equally well expect that the two areas would differ in their histological features. As a matter of fact, neither condition obtains in the light of available anatomical evidence.

Campbell (4), on the basis of cytoarchitectonic studies, divided the temporal cortex of the cat into two parts which he called ectosylvian A and ectosylvian B. (See Fig. 6.) Obviously, neither area corresponds to either of the areas described in the present study (*i.e.* primary projection area or pos-

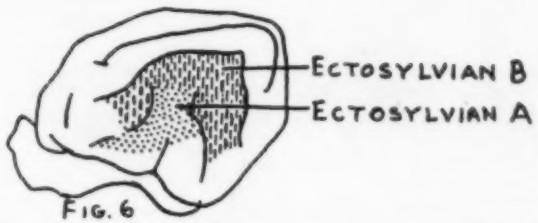


FIG. 6. Cat temporal areas according to Campbell.

terior ectosylvian secondary area). Mettler (6), in the course of an investigation of the cat's temporal region by the Marchi method, describes six cases in which his lesions involve considerable portions of the primary acoustic area as defined independently by Kornmüller (5), Bremer and Dow (3), and Ades (1). (See Fig. 7–12.) In four of the six cases, degenerated fibers to the area which has been designated as secondary acoustic are conspicuously absent; in the other two cases, such fibers are sparse, and, judging from Mettler's description, among the least striking of the short association connections from the middle ectosylvian cortex. In short, the areas delineated by both Campbell and Mettler fail to coincide with the experimental findings described above.

At this point it may be pertinent to note that the only point of agreement which can be found in the feline temporal area is on the location of the primary projection area. By the use of no less than four different methods, Kornmüller (5), Bremer and Dow (3), Woollard and Harpman (7), and Ades (1) define almost precisely the same primary projection area. There is, thus, a serious disagreement between the cortical map common to this group of workers and the map of Campbell which Mettler apparently finds himself able to confirm.

It is difficult to consider seriously any map which, like Campbell's, places acoustic function in the carnivore pseudosylvian cortex. That area corresponds to the insular cortex of the primate which is certainly not acoustic. The carnivore ectosylvian region, on the other hand, is presumably homologous with the superior temporal cortex of the primate, and the latter most

definitely is acoustic in its connections and function (2). In the light of the recent studies cited above it is clear that the termination of the geniculo-temporal radiation in the cat has as its lowest possible inferior limit, the superior end of the pseudosylvian sulcus; more probably the limit is 2–3 mm. above the end of the sulcus. The situation in the cat is complicated because

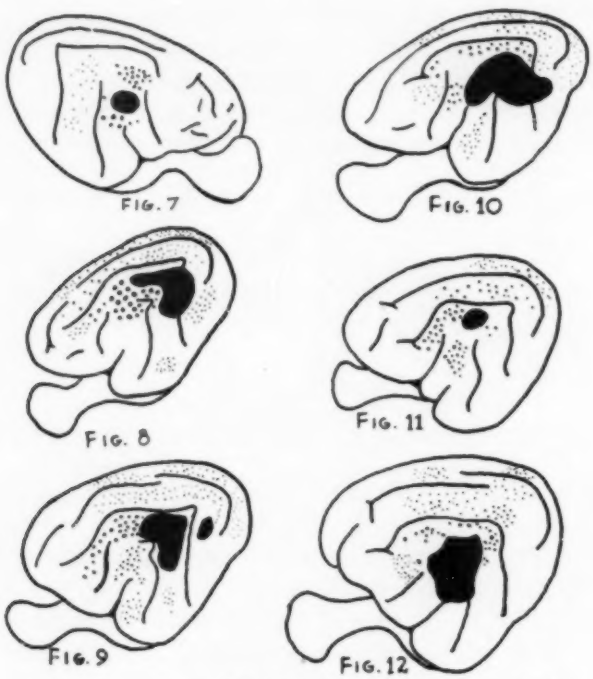


FIG. 7–12. After Mettler. Solid black marks lesions. Stippling indicates points of termination of degenerated fibers from area of lesion; proportionate number of fibers is shown by relative size of dots, heavy dots denoting strong connections.

FIG. 7. Mettler's cat 513, Fig. 13.
FIG. 8. Mettler's cat 515, Fig. 11.
FIG. 9. Mettler's cat 517, Fig. 11.
FIG. 10. Mettler's cat 514, Fig. 17.
FIG. 11. Mettler's cat 505, Fig. 21.
FIG. 12. Mettler's cat 507, Fig. 9.

of the complete lack of a middle ectosylvian sulcus, rendering problematical the exact line of demarcation between pseudosylvian and middle ectosylvian cortex. If compared with the canine temporal region, it seems most likely that the lower limit of the geniculo-temporal projection area of the cat corresponds to the middle ectosylvian sulcus of the dog (in the dog, the acoustically responsive area is confined to the cortex bounded inferiorly by the middle ectosylvian sulcus).

Since Campbell's map is apparently impossible of confirmation even by

his own method (3), it is no longer acceptable. If it be rejected, it is possible to reopen the problem of interrelations within the feline temporal cortex. Therefore, in addition to the primary projection area occupying the middle ectosylvian gyrus, the experiments reported here indicate the presence of a secondary acoustic area on the posterior ectosylvian gyrus.

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THE PSEUDAFFECTIVE STATE AND DECEREBRATE RIGIDITY IN THE SLOTH*

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THE EXCEEDINGLY low plane of activity on which the sloth lives offers a stimulating challenge to naturalists and experimental workers alike. In studying various functions of this animal recently in its native habitat (2), it seemed desirable to inquire into some phases of cerebral influence on muscular activity. Different ways of speeding up or deslothing the sloth, including excitation of the central nervous system, have already been reported (5). Such stimulation of this ancient mammal, however, does not bring it anywhere near par in a muscular sense with modern, active forms.

The commoner sloths, the two-toed *Cholepus hoffmanni*, and the extremely slow three-toed *Bradypus griseus griseus*, were studied in the present experiments. All observations refer commonly to both didactyl and tridactyl forms, unless otherwise noted.

METHODS

Under light preliminary ether anesthesia, a few square centimeters of the scalp in the mid-region were deflected, a 2-cm. trephine opening made in the cranium, and the rest of the bony vault then removed with rongeur forceps to expose the upper brain surface in its coverings. In earlier work some attempts were made to localize cortical motor areas by electrical stimulation, after cutting and drawing aside the dura mater; these efforts were much handicapped, however, under tropical conditions. More specific inquiry was then made into the possible occurrence of the pseudaffective state in both sloth forms. Cerebral transections were performed with a semi-blunt dissector, in order to reduce bleeding to a minimum. Since the blood pressure in the peripheral tissues of sloths is low (2), ligature of carotid vessels was not necessary. At autopsy the remaining brain tissues were removed and examined after fixation in formalin.

RESULTS

The first sections of the cerebral cortex extended over the frontal and parietal regions, and were carried to the depth of a few millimeters only. Shock was observed to supervene in all cases; the atonic, unresponsive condition was usually profound for about 5 minutes, and gradually gave way in the next 8 or 10 minutes to a nearly normal responsive state. In some cases, however, shock was in evidence for 20–30 minutes.

Such partially decorticate sloths became spontaneously active within an hour after operation, and began climbing about the cage or crawling awk-

* The physiological phases of these studies were carried out at the Gorgas Memorial Laboratory, Rep. Panama, under the terms of a John Simon Guggenheim Memorial Fellowship held by the senior author during 1937–39. The thanks of the authors are gratefully extended to Dr. Herbert C. Clark of this laboratory, for his unfailing courtesies during the investigations.

wardly along the floor. In general, however, voluntary movements of the animal at this time were even slower than normal for the sloth. Further section of the whole cortex was made usually within 2 hours, to the depth of several millimeters lower than the first incision.

The completely decorticate two-toed animal showed itself vigorously aggressive (for the sloth) on merely slight provocation: the flexion striking movement of the fore limbs was fairly quick and powerful, although erratic; teeth were bared, and clawing, biting and grinding actions ensued; snarling and hissing were common features, and continued many minutes after a suspected adversary had retreated. Salivation occurred in a few cases. Sweating was not observed on the foot-pads or any part of the body at any time. It may be mentioned, however, that at least vestigial sweat glands are said to be present in the sloth (2). The quasi-emotional expressions were usually lower in force value than affective reactions found in normal animals, but showed longer, irregular and unbridled continuance.

In the case of the three-toed sloth, pseudaffective responses were somewhat similar but much less vigorous, and striking movements were usually

Table 1. Decorticate and Decerebrate Reactions in Sloths

Animal No.	Species	Days Observed after Operation	Level of Brain Section	Rectal Temp. °C.	Pseudaffectivity	Dominant Rigidity	
						Flexion	Extension
1	2-Toed (Chol. hoff.)	2	Ant. Coll.	30.9	+++	+++	0
2	" "	4	Low	32.8–30.5	+++	+++	0
3	" "	7	Ant. Coll.	34.2–34.8	+++	+++	0
4	" "	6	Low	29.3–32.2	++	+	+++
5	" "	4	Post. Coll.	33.5–33.9	+	+	+++
6	" "	3	Post. Coll.	34.9–35.5	+	+++	+
7	" "	2	Ant. Coll.	34.0	+	+++	+
8	" "	6	Ant.-Post. C.	....	+	+	+
1	3-Toed (Brad. g. g.)	1	Low	....	0	+++	0
2	" " "	2	Low	32.9	+	+	+++
3	" " "	2	High	33.7	+	+	+++
4	" " "	6	Low	....	0	+	0

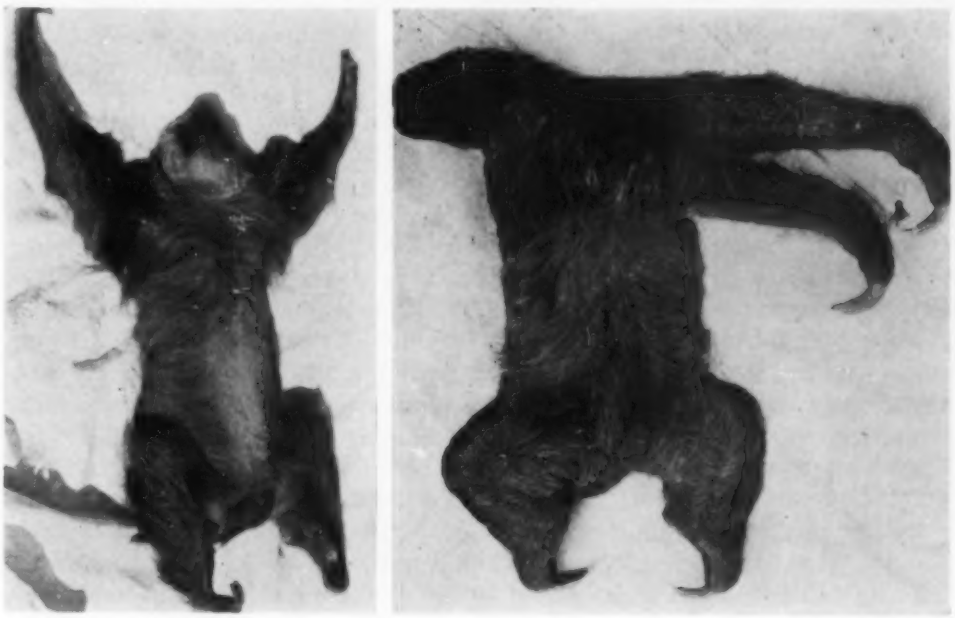
absent. The expressions were really in nearer agreement with the normal behavior of this most torpid of all mammalian types. The results of these experiments are given in summary in Table 1.

There was persistence of pseudaffectivity in nearly all animals even after several brain sections had been carried out, and the immediate consequent shock had disappeared. The condition was apparent to some extent after transections in the vicinity of the anterior colliculi. In the case of low-level or decerebrate preparations, however, such periods of (induced) activity ap-

peared only occasionally, and intermittent outbursts of rigidity were frequent.

In a few of the earlier experiments on decerebrate sloths, the rigidity which was first observed was wholly of the flexor type. The flexion movements were usually extreme, and the animal sometimes remained curled up in a resistant, ball-like mass for 5–15 minutes at a time. In a few instances the forelimbs only were held tightly clasped across the chest and abdominal area. In tridactyl animals, the stumpy tail was usually extended or dorsiflexed.

It was a common finding in many of these experimental animals, however, that decerebrate rigidity of the extensor type also supervened during a part of the post-operative period. In some cases, indeed, this was the dominant condition. The extensor position which was assumed was essentially



A B

Typical extensor rigidity in decerebrate sloths: (A) Two-toed animal, *Cholepus hoffmanni;* (B) Three-toed, *Bradypus griseus griseus*. Note that feet are held in the position of slight flexion. The hind limbs of both species are not straight even in the "fully extended" position.

similar in both didactyl and tridactyl forms, although *Cholepus* usually gave the better display; both fore and hind limbs were involved, and dorsiflexion of the head was seen when the animal was placed on its side and thus allowed freer movement. Slight flexion of the feet occurred almost invariably in correlation with extension of the limbs. In several instances extensor rigidity appeared more prominently in the latter part of the post-operative survival period, when in contrast flexion usually tended to disappear.

Some features of the posture in the decerebrate preparation are shown in the adjoining illustrations (Fig. 1). Decerebrate sloths survived several days —in some cases 6 or 7—after cerebral section had been carried out. No attempt was made to maintain asepsis, and apparently infections were responsible in a few instances for early exitus.

Rectal temperatures were recorded throughout, and it will be seen from Table 1 that no marked change followed decerebration. Earlier work in this laboratory shows that the rectal temperature of sloths is normally several degrees below that of higher mammals (3, 4, 5), and those now recorded are in agreement. The average readings in our experiments were:

normal two-toed sloth,	34.4°; three-toed, 33.0°.
decerebrate two-toed sloth,	33.0°; three-toed, 33.3°

Pulse and respiratory rates were not significantly different from those of the normal, unoperated sloth.

Discussion

The sum total of the decorticate reactions in the sloth constituted a fairly complete parallel to the pseudaffective or quasi-emotional state first observed by Woodworth and Sherrington (9). Similar in character, pseudaffectivity in this ancient and primitive form was less evident in degree only compared to that described in higher mammals by Cannon and Britton (6).

Decerebrate rigidity of the extensor type occurred frequently in these experiments, but not as often as the flexor type, which was first described by Richter and Bartemeier (8). These earlier investigators did not observe extensor rigidity in the sloth, possibly because of failure to study their preparations over a sufficient long period after operation. In four of our surviving cases, hypertonus in extension became a notable feature as the condition of flexion regressed. Bazett and Penfield (1) also found differences in the character of tonic decerebrate responses at different periods after operation. Furthermore, our animals were utilized in the fresh state in the tropics, shortly after being brought in from the jungle.

The extensor rigidity appeared to be typical or classical in character, not unlike that in the decerebrate cat. Differences in the response of the decerebrate sloth, *i.e.* flexion or extension under varying conditions, may perhaps be referable to the level of brain section, but on this point our results are not clear.

Langworthy (7) showed that, although the flexors in sloths may represent the anti-gravity muscles, extensor responses of the limbs on stimulation of the cortical motor areas are nevertheless predominant. That the muscle mass of the commoner tardigrades represents only about 25 per cent of the body weight, compared to 40 per cent in most mammals, has already been pointed out (2). The marked hypertonicity which may be developed in the decerebrate sloth is therefore particularly striking, in view of the relative poverty of skeletal muscle in this animal.

Summary

1. Shock which follows transection of the brain in the sloth is profound for about 5 minutes, and usually disappears in 10–15 minutes.

2. Considerable activity, apparently spontaneous, is shown by sloths which have been deprived of large cortical areas, including those dominating motor reactions in higher forms.

3. A pseudaffective state, not significantly different from that observed in higher mammals, appears following removal of the upper parts of the tardigrade cortex. This condition may persist even after brain section has been made to low levels.

4. Decerebrate rigidity in the sloth may be either flexor or extensor in type; the former is somewhat more frequent. Extensor rigidity is usually more evident during the latter part of the post-operative survival period, and is classical in type.

5. Temperature, pulse and respiratory rates were well maintained in the decerebrate sloth.

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